

Natalizumab: A Review of Its Use in the Management of Relapsing-Relmitting Multiple Sclerosis

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Published online: 3 August 2013
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Abstract Natalizumab (Tysabri®) is a humanized monoclonal antibody against the $\alpha 4$ chain of integrins and was the first targeted therapy to be approved for the treatment of relapsing-relmitting multiple sclerosis (RRMS). Natalizumab acts as a selective adhesion molecule antagonist, which binds very late antigen (VLA)-4 and inhibits the translocation of activated VLA-4-expressing leukocytes across the blood–brain barrier into the CNS. In a pivotal phase III clinical trial, natalizumab 300 mg intravenously every 4 weeks for 2 years in adults with RRMS significantly reduced the annualized relapse rate and the risk of sustained progression of disability compared with placebo, as well as significantly increasing the proportion of relapse-free patients at 1 and 2 years. Natalizumab also significantly reduced the number of T₂-hyperintense, gadolinium-enhancing and T₁-hypointense lesions on magnetic resonance imaging, and significantly

reduced the volume of T₂-hyperintense and T₁-hypointense lesions compared with placebo. Natalizumab recipients generally experienced improved health-related quality of life at 1–2 years. Natalizumab was generally well tolerated in pivotal trials. The only adverse events that were more frequent with natalizumab monotherapy than with placebo were fatigue and allergic reactions. The main safety and tolerability issue with natalizumab is the incidence of progressive multifocal leukoencephalopathy (PML). As long as the risk of PML is managed effectively, natalizumab is a valuable therapeutic option for adults with highly active relapsing forms of multiple sclerosis.

Natalizumab in relapsing-relmitting multiple sclerosis: a summary

Humanized monoclonal antibody targeted against the $\alpha 4$ chain of integrins

First targeted disease-modifying therapy approved for the treatment of adults with relapsing-relmitting multiple sclerosis

Significantly reduces annualized relapse rate and the risk of sustained progression of disability over 2 years compared with placebo

Significantly increases the proportion of relapse-free patients at 1 and 2 years

Reduces the number of T₂-hyperintense and T₁-hypointense lesions on magnetic resonance imaging at 1 and 2 years

Improves most patients' health-related quality of life at 1 and 2 years

Generally well tolerated, but uncommonly causes progressive multifocal leukoencephalopathy

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1 Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the CNS that is thought to result from an autoimmune reaction to self-antigens in the CNS in genetically susceptible individuals, although no responsible self-antigens have yet been unequivocally identified [1]. The disease process is believed to start with increased migration of autoreactive lymphocytes across the blood–brain barrier [2]. MS is characterized by multifocal localized inflammation causing loss of oligodendrocytes, demyelination of nerves and axonal damage, which leads to progressive neurological degeneration [1]. Histologically, the foci of inflammation and demyelination produce sclerotic plaques (lesions) in the CNS, predominantly in the white matter of the brain, brainstem, spinal cord and optic nerve sheaths, although more diffuse damage also occurs throughout the brain and spinal cord [3]. Clinical signs and symptoms vary, but commonly include paraesthesia or numbness, motor weakness, visual disturbances and lack of coordination [4]. MS typically occurs in young adults (aged 20–40 years), with a twofold higher incidence in women than in men, and is estimated to affect approximately 2.5 million individuals worldwide [5].

The course of MS is variable, but the most common form at initial diagnosis (≈ 80 – 85 % of patients) is relapsing-remitting MS (RRMS), which begins with an initial clinically isolated syndrome (CIS) and, following conversion to clinically definitive MS, is characterized by subsequent discrete exacerbations (relapses) followed by complete or partial recovery (remissions), with a lack of disease progression between relapses [1, 2]. Relapses generally occur at a frequency of ≤ 1.5 per patient/year [2]. RRMS eventually develops into secondary progressive MS (SPMS) in a high proportion of patients, with steady, irreversible progression of clinical disability [2]. In approximately 10–15 % of patients, the disease is progressive from onset, with few, if any, relapses (flare-ups), remissions or plateaus (primary progressive MS), while in a very small proportion of patients the disease is progressive from onset, but with relapses from which there is significant recovery, although symptoms worsen between relapses (progressive relapsing MS) [2]. The relationship between relapse rates and the accumulation of disability in RRMS is not clear, but the predominant determinant of irreversible disability is the onset of secondary progressive disease [6, 7].

Pharmacotherapies for RRMS have been aimed at symptomatic treatment (e.g., treating spasticity and bladder dysfunction), treating acute relapses, reducing the frequency and severity of relapses, and delaying progression. High-dose intravenous corticosteroid (methylprednisolone)

therapy reduces the duration of relapse, but does not affect the degree of recovery or the long-term accumulation of disability [8]. Conventional immunosuppressive agents (e.g., cyclophosphamide, methotrexate, azathioprine and cyclosporin) generally display only limited success in altering the disease process [8]. Mitoxantrone is very active, but is toxic and, therefore, usually reserved for patients with particularly aggressive disease [8]. The newer immunomodulatory agents interferon- β and glatiramer acetate are partially effective disease-modifying agents, reducing the annualized relapse rate by ≈ 30 % for 2–3 years and reducing or delaying the accumulation of disability; they have been the mainstay of pharmacotherapy for many years [2, 8–10].

Natalizumab (Tysabri[®]) is the first targeted agent to be approved for the treatment of RRMS [11]. It is a humanized monoclonal antibody targeted against the $\alpha 4$ chain of integrins and acts as a selective adhesion molecule antagonist, which inhibits the translocation of leukocytes across blood vessel membranes, particularly the blood–brain barrier with regard to MS. All administration of natalizumab was voluntarily suspended by the manufacturer after two patients with MS developed progressive multifocal leukoencephalopathy (PML), an opportunistic infection of the brain with the JC virus, during or shortly after treatment with natalizumab in combination with interferon β -1a in an investigational clinical trial. The risk for PML with natalizumab was considered to be low (1 in 1,000) [12] and the drug was subsequently approved in the EU as single disease-modifying therapy in patients with highly active RRMS refractory to interferon- β (now amended to also include glatiramer acetate [13]) or in patients with rapidly evolving, severe disease [11].

This article reviews the efficacy and tolerability of natalizumab in the treatment of RRMS and overviews its pharmacological properties.

2 Pharmacodynamic Properties

Integrins are transmembrane receptors governing the attachment of cells to surrounding tissues and extracellular matrix, and are also involved in cell signaling [14]. They are heterodimers of various α and β chains. The $\alpha 4$ (CD49d) chain associates with either the $\beta 1$ (CD29) chain to form the $\alpha 4\beta 1$ integrin (also known as very late antigen [VLA]-4) or with the $\beta 7$ chain to form the $\alpha 4\beta 7$ integrin (also known as lymphocyte Peyer's patch adhesion molecule [LPAM]-1) [14]. VLA-4 is expressed on the plasma membranes of all leukocytes, except neutrophils [11, 14]. When activated, VLA-4 undergoes a conformational change that allows it to bind with high avidity to its natural ligands, vascular cell adhesion molecule-1 (VCAM-1) on

vascular endothelial cells and fibronectin in the extracellular matrix [14]. VLA-4 is a critical adhesion molecule involved in regulating the trafficking of mononuclear leukocytes from the peripheral circulation to sites of inflammation.

Natalizumab is a humanized IgG4 monoclonal antibody directed against the $\alpha 4$ chain of integrins (i.e., $\alpha 4\beta 1$ [VLA-4] and $\alpha 4\beta 7$ [LPAM-1]) [11]. Its putative primary activity related to its beneficial effects in patients with MS is to prevent the interaction of VLA-4 with VCAM-1 on endothelial cells and thereby prevent diapedesis, particularly the extravasation of activated leukocytes across the blood–brain barrier into the CNS [11]. By blocking diapedesis, natalizumab limits the immune and inflammatory processes in the brain, and results in accumulation of leukocytes in the peripheral blood. Natalizumab also blocks the interaction of $\alpha 4$ -expressing leukocytes with the connecting segment (CS)-1 isoform of fibronectin and osteopontin, which may further limit leukocyte recruitment, migration and activity in the brain [11]. It is thought that natalizumab may also have other effects on the immune and haematopoietic systems [15].

Natalizumab blocks the interaction of the $\alpha 4\beta 7$ integrin with endothelial mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and interferes with the homing of lymphocytes to gastrointestinal lymphoid tissue—hence, its use in treating Crohn's disease (an approved indication in the US) [16].

The low-grade blood–brain barrier leakage detected by magnetic resonance imaging (MRI) in visibly non-enhancing lesions in patients with RRMS was shown not to be mediated by VLA-4, since the leakage was not significantly lower in patients treated with natalizumab compared with placebo recipients in the pivotal phase III AFFIRM trial (see Sect. 4.1 for trial details) [17].

Patients with MS displayed mild CSF pleocytosis compared with a cohort of patients with neurological disease other than MS [18]. Natalizumab treatment for a median of 30 doses in patients with MS ($n = 23$) was shown to significantly reduce the total white blood cell count ($p < 0.0001$), $CD4^+$ T cells ($p < 0.0001$), $CD8^+$ T cells ($p < 0.0001$), $CD19^+$ B cells ($p < 0.0001$) and $CD138^+$ plasma cells ($p < 0.01$) in the CSF compared with MS patients not treated with natalizumab [18]. The CSF total white blood cells, $CD4^+$ T cells, $CD8^+$ T cells, $CD19^+$ B cells and $CD138^+$ plasma cells remained significantly (all $p < 0.0001$) lower in natalizumab-treated patients than in MS patients not treated with natalizumab at 6 months after the cessation of therapy [18]. Natalizumab reduced CSF $CD4^+$ T cells more than $CD8^+$ T cells, such that the $CD4^+/CD8^+$ ratio was significantly ($p < 0.001$) reduced in the CSF versus that in the CSF of MS patients not treated with natalizumab, but was not reduced in the

peripheral blood [19]. The $CD4^+/CD8^+$ ratio in the CSF of patients treated with natalizumab was similar to that in the CSF of HIV-infected patients [19].

An analysis of autopsy tissue preparations from a patient who developed PML during natalizumab therapy, compared with samples from patients (with or without MS) who had not been treated with natalizumab, indicated that natalizumab therapy significantly reduced the number of antigen-presenting cells ($CD209^+$ dendritic cells) [$p < 0.01$] and the expression of major histocompatibility complex class II molecules ($p < 0.05$), as well as eliminating $CD4^+$ T cells, in cerebral perivascular spaces [20]. Treatment of RRMS patients with natalizumab reduced the expression of VLA-4 on peripheral blood dendritic cells, tended to reduce the proportion of plasmacytoid dendritic cells and impaired the interaction between plasmacytoid dendritic cells and $CD4^+$ T cells in vitro compared with healthy controls or MS patients not treated with natalizumab [21].

Natalizumab therapy caused almost complete reduction of detectable VLA-4 on peripheral blood T cells, B cells, NK cells and monocytes, and also produced a significant decrease in soluble VCAM-1 (most probably by down regulation of membrane-bound VCAM-1) in serum, beginning within 4 weeks of starting therapy and maintained throughout therapy for 24 months [22]. Soluble VCAM-1 levels were higher in samples containing neutralizing antibodies to natalizumab and did not differ significantly from control samples (i.e., from healthy volunteers or MS patients not treated with natalizumab). In one patient who developed high-titre neutralizing antibodies to natalizumab, soluble VCAM-1 levels returned to baseline values [22].

In patients with RRMS ($n = 19$) treated with natalizumab 300 mg intravenously every 4 weeks, there was no inhibition of cytokine production in the systemic circulation [23]. The number of cells secreting the proinflammatory cytokines tumour necrosis factor- α (TNF- α) and interferon γ (IFN- γ) actually increased over 6 months, as did the level of TNF- α messenger RNA in peripheral blood mononuclear cells [23].

Natalizumab therapy increased the proportion of $CD4^+$ T cells and $CD8^+$ T cells producing proinflammatory cytokines (e.g., TNF- α , IFN- γ , interleukin [IL]-17, IL-2) in peripheral blood, either as a result of preventing egress of activated T cells from the peripheral circulation and/or by natalizumab-induced T cell activation [24]. Natalizumab therapy appears to be associated with a T helper cell proinflammatory Th1 cytokine response in peripheral blood, unlike glatiramer acetate, which produces a switch to a predominantly anti-inflammatory Th2 cytokine response [15]. One study found that $CD4^+$ T cells reactive to myelin basic protein were not selectively enriched in the peripheral

blood of patients treated with natalizumab [25]. Peripheral blood CD4⁺ T cells from healthy volunteers that were activated and exposed to natalizumab in vitro produced mild upregulation of IL-2, IFN- γ and IL-17 expression, suggesting a direct signalling effect of natalizumab [26]. CD4⁺ T cells isolated from the peripheral blood of patients with RRMS 24 h after the very first dose of natalizumab showed partial loss of VLA-4 from their surface and already displayed increased production of IL-2, IL-17 and IFN- γ [26].

In addition to increases in T cells in the peripheral blood of RRMS patients treated with natalizumab, there are also increases in mature B cells [27], CD19⁺CD10⁺ pre-B cells [27, 28], NK cells [29] and CD34⁺ haematopoietic stem cells [29, 30]. The number of CD34⁺ stem cells in bone marrow is also increased approximately 10-fold [31]. Natalizumab appears to mobilize a different CD34⁺ stem cell subset to that mobilized by granulocyte-colony stimulating factor (G-CSF) [31]. The increase in CD34⁺ stem cells in peripheral blood appears to result from impaired homing to bone marrow, rather than to mobilization from bone marrow [32].

The RESTORE study enrolled patients who had been treated successfully (i.e., no relapses or gadolinium-enhancing MRI lesions) with natalizumab for at least the previous 12 months and compared continuation of natalizumab treatment with interruption of treatment for 24 weeks [33]. Patients in the interruption arm switched from natalizumab to placebo or alternative immunomodulatory therapy (interferon β -1a, glatiramer acetate or methylprednisolone). Within 4 months of treatment interruption, serum VLA-4 levels, soluble VCAM levels and circulating lymphocyte subsets, including CD34⁺ cells, returned to levels consistent with those seen in patients not treated with natalizumab [33]. This immune reconstitution paralleled the return of disease activity as measured by brain MRI.

Neurofilament light (NFL) in the CSF was shown to be a useful biomarker of axonal damage, being elevated approximately threefold in patients with active MS (90 % RRMS) [$n = 92$] [34]. Natalizumab therapy for 6–12 months reduced the levels of NFL in CSF back to levels not significantly different from those in healthy controls. In contrast, glial fibrillary acidic protein was not elevated in patients with RRMS and was unaffected by natalizumab therapy, suggesting it is more a marker of progressive phases of the disease [34].

In neonates of two women treated with natalizumab until the 34th week of pregnancy, in vitro CXCL12-induced chemotaxis of peripheral blood T cells was reduced, suggesting that natalizumab therapy during pregnancy may possibly compromise the host defence in newborns, although normal chemotaxis was restored by 12 weeks of age [35].

3 Pharmacokinetic Properties

Data on the pharmacokinetic properties of natalizumab come from a single-dose (0.03–3.0 mg/kg intravenously) study in patients ($n = 28$) of mean age 41 years with MS (71 % RRMS, 29 % SPMS) [36] and a study of the effects of plasma exchange on the clearance of natalizumab in patients ($n = 12$) of mean age 41 years with RRMS who had received at least three doses of natalizumab 300 mg by intravenous infusion every 4 weeks [37]. All other data are derived from the European Medicines Agency's summary of product characteristics for natalizumab [11] or the manufacturer's US prescribing information [16].

Single-dose natalizumab 0.3, 1.0 and 3.0 mg/kg infused intravenously over 45 min produced detectable dose-proportional serum concentrations for 1, 3 and 8 weeks, respectively; serum concentrations for lower doses rapidly declined below the limit of detection [36]. Single-dose natalizumab 3.0 mg/kg produced a mean maximum plasma concentration ($C_{\max}$) of 52.5 $\mu\text{g/mL}$ after a mean time ($t_{\max}$) of 2.07 h. The mean area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) was 9,899.1 $\mu\text{g}\cdot\text{h/mL}$ for this dose and the mean steady-state volume of distribution was 67.1 mL/kg [36]. The mean clearance for the 3.0 mg/kg dose was 0.3 mL/h/kg and the mean terminal half-life ($t_{1/2}$) was 108 h. Mean volume of distribution and clearance decreased with increasing dose, while $t_{1/2}$ increased with increasing dose [36]. Low-titre anti-natalizumab or anti-idiotypic antibody were detected in three patients in the 3.0 mg/kg dose group.

Following repeated intravenous infusions of natalizumab 300 mg, the mean $C_{\max}$ was 110 $\mu\text{g/mL}$, the predicted time to steady state was ≈ 36 weeks (also cited as 24 weeks with 4-weekly dosing [16]) and the mean average steady-state trough concentrations were 23–29 $\mu\text{g/mL}$ [11]. The mean volume of distribution was 5.7 L, the mean clearance was 16 mL/h and the mean $t_{1/2}$ was 11 days [16].

A population survey of MS patients ($n > 1,100$) receiving natalizumab 3–6 mg/kg (over half of whom received a fixed 300 mg dose as monotherapy) found the mean steady-state clearance to be 13.1 mL/h and the mean $t_{1/2}$ to be 16 days [11]. Clearance increased non-proportionally with increasing bodyweight, but the change was not clinically significant. The presence of persistent anti-natalizumab antibodies increased the clearance of natalizumab approximately threefold [11].

The pharmacokinetics of natalizumab have not been assessed in subjects with renal or hepatic impairment [11].

Patients with MS on stable natalizumab therapy ($n = 12$) underwent three plasma exchange sessions (each of $1.5 \times$ plasma volume over 2.5–3 h) over 5–8 days starting 10–14 days after a natalizumab dose [37]. After the first session, the serum concentration of natalizumab

decreased by a mean of 82 %, but re-equilibrated within 24 h to a mean reduction of 65 %. At one week after the third plasma exchange session, the mean serum concentration of natalizumab was 3.2 µg/mL, representing a mean reduction of 92 % from baseline. The mean natalizumab serum concentration at four weeks after the three plasma exchange sessions was reduced by 75 % compared with patients not undergoing plasma exchange ($p = 0.002$) [37]. From these results it was estimated that five plasma exchange sessions of $1.5 \times$ plasma volume would reduce the serum natalizumab concentration to <1 µg/mL in >95 % of patients—a reduction that would take 97 days without plasma exchange. Plasma exchange did not affect the level of VLA-4 saturation on peripheral blood mononuclear cells, unless the serum concentration of natalizumab was reduced below 1 µg/mL, at which point saturation decreased to <50 % [37].

Natalizumab is excreted in human milk; therefore, breast-feeding is not recommended during treatment [11].

4 Therapeutic Efficacy

Data on the efficacy of natalizumab in the treatment of adult patients with RRMS are available from two fully published, large, randomized, double-blind, placebo-controlled, multicentre, phase III trials: AFFIRM (Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis) [38] and SENTINEL (Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis) [Sects. 4.1 and 4.2] [39]. In addition, there are two large, ongoing, long-term, open-label, observational studies of note for which data (published in preliminary form only) are available: STRATA (Safety of Tysabri Re-dosing and Treatment) [40, 41] and TOP (Tysabri Observational Program) [Sect. 4.3] [42].

4.1 Phase III Trials

AFFIRM compared the efficacy of natalizumab monotherapy (300 mg intravenously every 4 weeks) with placebo for ≥ 2 years in patients aged 18–50 years with RRMS ($n = 942$) [38]. SENTINEL compared the addition of natalizumab (300 mg intravenously every 4 weeks) versus placebo to existing interferon β -1a therapy in patients aged 18–55 years with RRMS ($n = 1,171$) who had been receiving interferon β -1a (30 µg intramuscularly once weekly) for at least the previous 12 months [39]. In both studies, patients had to have had at least one medically documented relapse in the previous 12 months, had a baseline score on the Kurtzke Expanded Disability Status Scale (EDSS; score range 0–10 with higher scores

indicating greater disability) between 0 and 5 (mean 2.3 in AFFIRM and 2.4 in SENTINEL), and had MRI lesions consistent with a diagnosis of MS.

Mean annualized relapse rates over the previous year at baseline were 1.52 for AFFIRM and 1.47 for SENTINEL. In AFFIRM and SENTINEL, respectively, the mean ages of patients were 36.0 and 38.9 years, while 70 and 74 % were female [38, 39]. At baseline, the proportions of patients with ≥ 9 hyperintense lesions on T₂-weighted MRI were 95 % in AFFIRM and 89 % in SENTINEL. The mean number of gadolinium-enhancing lesions at baseline in the two studies were 2.2 (range 0–39) and 0.9 (range 0–24), respectively [38, 39].

In both studies, the primary endpoint at 1 year was the annualized relapse rate and the primary endpoint at 2 years was the cumulative probability of sustained progression of disability, which was defined as an increase of ≥ 1.0 in EDSS score (sustained for 12 weeks) from a baseline score of ≥ 1.0 or an increase of ≥ 1.5 in EDSS score (sustained for 12 weeks) from a baseline score of zero [38, 39].

4.1.1 AFFIRM

In AFFIRM, natalizumab significantly ($p < 0.001$) reduced the risk of sustained progression by 42 % compared with placebo at 2 years and significantly ($p < 0.001$) reduced the annualized relapse rate by 68 % at 1 year (Table 1) [38]. The reduction in annualized relapse rate was sustained at 2 years and the proportions of patients free of relapse were significantly ($p < 0.001$) higher with natalizumab than with placebo at both 1 and 2 years (Table 1).

Natalizumab significantly ($p < 0.001$) reduced the number of new or enlarging hyperintense lesions on T₂-weighted MRI compared with placebo by 80 % at 1 year and by 83 % at 2 years (Table 1) [38]. At 2 years, 57 % of natalizumab recipients had no new or enlarging T₂-hyperintense lesions compared with 15 % of placebo recipients. Likewise, natalizumab significantly ($p < 0.001$) reduced the number of gadolinium-enhancing lesions by 92 % at both 1 and 2 years compared with placebo, and 97 % of natalizumab recipients compared with 72 % of placebo recipients were free of lesions detected by gadolinium-enhanced MRI at 2 years (Table 1).

In addition, natalizumab significantly ($p < 0.001$) reduced the number of new T₁-hypointense lesions by 74 % at 1 year and by 83 % at 2 years compared with placebo, and significantly ($p < 0.001$) reduced the mean number of new non-enhancing T₁-hypointense lesions on gadolinium-enhanced scans by 68 % at 1 year and by 79 % at 2 years [43]. Natalizumab also significantly ($p < 0.001$) reduced both T₂-hyperintense and T₁-hypointense lesion volumes compared with placebo over 2 years [43].

Table 1 Efficacy of intravenous natalizumab 300 mg every 4 weeks in adult patients with relapsing-remitting multiple sclerosis. Results from the randomized, double-blind, placebo-controlled, multicentre, phase III, AFFIRM [38] and SENTINEL [39] trials

	AFFIRM		SENTINEL	
	NAT (<i>n</i> = 627)	PL (<i>n</i> = 315)	NAT + IFNβ-1a (<i>n</i> = 589)	PL + IFNβ-1a (<i>n</i> = 582)
Clinical endpoints				
Mean annualized relapse rate at 1 year ^a	0.26**	0.81	0.38**	0.82
Mean annualized relapse rate at 2 years	0.23**	0.73	0.34**	0.75
Cumulative probability of sustained progression of disability at 2 years (%) ^b	17**	29	23*	29
Absence of relapse at 1 year (% of pts)	80**	60	72**	51
Absence of relapse at 2 years (% of pts)	72**	46	61**	37
MRI-related endpoints				
Mean no. of new or enlarging T ₂ -hyperintense lesions/pt at 1 year	1.2**	6.1	0.5**	2.4
Mean no. of new or enlarging T ₂ -hyperintense lesions/pt at 2 years	1.9**	11.0	0.9**	5.4
Absence of new or enlarging T ₂ -hyperintense lesions at 1 year (% of pts)	61	23	72	43
Absence of new or enlarging T ₂ -hyperintense lesions at 2 years (% of pts)	57	15	67	30
Mean no. of Gd-enhancing lesions at 1 year	0.1**	1.3	0.1**	0.8
Mean no. of Gd-enhancing lesions at 2 years	0.1**	1.2	0.1**	0.9
Absence of Gd-enhancing lesions at 1 year (% of pts)	96	68	96	75
Absence of Gd-enhancing lesions at 2 years (% of pts)	97	72	96	75

Gd gadolinium, IFN interferon, MRI magnetic resonance imaging, NAT natalizumab, no. number, PL placebo, pts patients. * $p < 0.05$, ** $p < 0.001$ versus PL or IFNβ-1a

^a Primary endpoint at 1 year

^b Primary endpoint at 2 years. AFFIRM, hazard ratio (HR) 0.58, 95 % CI 0.43–0.77. SENTINEL, HR 0.76, 95 % CI 0.61–0.96

Post hoc analysis of AFFIRM data showed that 64 % of natalizumab recipients compared with 39 % of placebo recipients were free of clinical disease activity (defined as no relapses and no progression of disability, sustained for 12 weeks) at 2 years ($p < 0.0001$) and 58 % of natalizumab recipients compared with 14 % of placebo recipients were free of radiological disease activity (defined as no gadolinium-enhancing lesions and no new or enlarging T₂-hyperintense lesions) at 2 years ($p < 0.0001$) [44]. Overall, 37 % of natalizumab recipients and 7 % of placebo recipients were free of both clinical and radiological disease activity at 2 years ($p < 0.0001$) [44]. When stratified by baseline disease activity, the proportion of placebo recipients free of both clinical and radiological disease activity was lower in those with highly active disease than in those with non-highly active disease (3.6 vs. 15.4 % in year 2). Since the proportions of natalizumab recipients free of both clinical and radiological disease activity were closer between the highly active and non-highly active disease cohorts in year 2 (65.0 vs. 69.5 %), those with highly active disease seemed to gain particular benefit from natalizumab therapy [44].

Using low-contrast 7-letter acuity tests, natalizumab produced a 39 % increase in the cumulative probability of sustained visual improvement by 120 weeks compared with placebo at 1.25 % contrast (32.5 vs. 25.0 %; hazard

ratio [HR] 1.39, 95 % CI 1.07–1.82; $p = 0.014$) and a 57 % increase at 2.5 % contrast (21.7 vs. 14.0 %; HR 1.57, 95 % CI 1.11–2.22; $p = 0.012$) [45]. Treatment differences first became apparent at 24 weeks after starting therapy. The low-contrast 5- and 10-letter acuity tests, as well as high-contrast visual acuity, did not show significant treatment differences [45].

4.1.2 SENTINEL

The addition of natalizumab to interferon β-1a in the SENTINEL study significantly ($p = 0.02$) reduced the risk of sustained progression of disability at 2 years by 24 % compared with the addition of placebo to interferon β-1a (i.e., interferon β-1a alone) and significantly ($p < 0.001$) reduced the annualized relapse rate by 54 % at 1 year (Table 1) [39]. The reduction in annualized relapse rate with combination therapy was sustained at 2 years, such that significantly ($p < 0.001$) more patients on combination therapy than on interferon β-1a alone were free of relapse at both 1 and 2 years (Table 1).

Combination therapy significantly ($p < 0.001$) reduced the number of new or enlarging T₂-hyperintense lesions by 83 % and the number of gadolinium-enhancing lesions by 89 % over 2 years compared with interferon β-1a alone [39] (Table 1). At 2 years, 67 and 96 % of combination

recipients were free of new or enlarging T₂-hyperintense lesions and gadolinium-enhancing lesions, respectively, compared with 30 and 75 %, respectively, of patients receiving interferon β -1a alone (Table 1).

Combination therapy significantly reduced the cumulative probability of sustained visual loss compared with interferon β -1a alone using the low-contrast 10-letter acuity test at 1.25 % contrast (HR 0.72, 95 % CI 0.54–0.98; $p = 0.038$), but not at 2.5 % contrast (HR 0.82, 95 % CI 0.57–1.18; $p = 0.29$) [46].

4.2 Health-Related Quality of Life

Health-related quality of life (HR-QOL) in patients treated with natalizumab has been assessed in the pivotal AFFIRM and SENTINEL clinical trials [47] and in clinical surveys reflecting real-world clinical practice [48, 49].

4.2.1 AFFIRM and SENTINEL Trials

Changes in HR-QOL during treatment with natalizumab were assessed using the Short Form-36 Survey (SF-36) administered as part of the Multiple Sclerosis Quality of Life Inventory in patients who participated in the AFFIRM and SENTINEL studies ($n = 2,113$) [47]. In total, 1,859 patients completed these studies and 251 withdrew; three randomized patients never received treatment, but were included in the HR-QOL analyses [47].

RRMS was associated with reduced HR-QOL, since the SF-36 physical component summary (PCS) and mental component summary (MCS) mean scores (43.2 and 47.0, respectively) at baseline were below the normal values for the general US population (mean score of 50.0) [47]. Baseline PCS scores were significantly ($p < 0.005$) lower in patients with EDSS scores ≥ 2 than in patients with EDSS scores of 0.0. Regression analysis showed that higher baseline EDSS scores and lower baseline Multiple Sclerosis Functional Composite scores were incrementally associated with significantly ($p < 0.001$) lower PCS and MCS scores. Similarly, higher baseline T₂-hyperintense and T₁-hypointense lesion volumes were each associated with significantly ($p < 0.05$) lower PCS and MCS scores [47]. However, the volume of gadolinium-enhancing lesions was not significantly associated with HR-QOL at baseline.

In placebo recipients, ≥ 1 relapse during the study period was associated with significant ($p < 0.0001$) reductions in SF-36 PCS scores in patients who were free of relapse at the time of assessment (24, 52 and 104 weeks) [47]. The PCS scores were lower still if the assessment was made while the patients were suffering a relapse. In contrast, PCS scores improved from baseline in those not experiencing any relapse. Regression analysis indicated that each relapse

was associated with a significant ($p < 0.001$) reduction of 1.3 points in PCS change from baseline score at week 104, while the effects on MCS change from baseline scores were not significant [47].

Natalizumab therapy was associated with significantly higher mean PCS scores than placebo at 24 ($p < 0.05$), 52 ($p < 0.001$) and 104 ($p < 0.01$) weeks in AFFIRM, while natalizumab plus interferon β -1a was associated with significantly higher mean PCS scores than placebo plus interferon β -1a at 52 ($p < 0.05$) and 104 ($p < 0.001$) weeks in SENTINEL [47]. MCS scores were higher with natalizumab than with placebo at all post-baseline time points in AFFIRM and with natalizumab plus interferon β -1a than with placebo plus interferon β -1a at all time points in SENTINEL, but only the difference between natalizumab and placebo at 104 weeks in AFFIRM reached statistical significance ($p = 0.011$) [47].

Active therapy with natalizumab was associated with significant ($p < 0.05$ – 0.001) improvements compared with placebo at 2 years in the two component summary scores and six of the eight individual scales (all except Bodily Pain and Mental Health) in AFFIRM, and in the PCS score and five of the eight individual scales (all except Bodily Pain, Role-Emotional and Mental Health) in SENTINEL [47].

A higher proportion of patients receiving natalizumab than placebo achieved a clinically important improvement (i.e., ≥ 0.5 -standard deviation change from baseline to week 104) for PCS (24.9 vs. 16.8 %) and MCS (28.5 vs. 21.6 %) in AFFIRM, and for PCS (23.3 vs. 17.4 %), but not MCS (17.1 vs. 21.0 %) in SENTINEL, although only the differences for PCS were statistically significant [47].

4.2.2 Clinical Surveys

A survey of MS patients ($n = 451$) who had received their third infusion of natalizumab via the TOUCH[®] (Tysabri[®] Outreach Unified Commitment to Health) prescribing programme in the US found that the majority of patients either maintained stable disease (51 %) or showed improvement in overall HR-QOL (46 %) as reported on a 3-point scale (improved, stable or worse) [48]. Improvement was significantly ($p = 0.008$) associated with shorter duration of disease (< 5 years). Functional Status (FS; 1–5 scale with higher numbers indicating greater limitation in functioning) was lower after natalizumab versus baseline (mean 2.43 vs. 2.76), with 30 % of patients having improved FS and 67 % of patients having stable FS [48]. Similarly, > 80 % of patients reported improvement in ≥ 1 physical item of the 29-item Multiple Sclerosis Impact Scale (MSIS-29) [particularly the ability to perform physically demanding tasks] and 75 % reported improvement in ≥ 1 psychological item (particularly feeling unwell) [48].

A Swedish survey on the effect of 50 weeks of treatment with natalizumab on the capacity of MS patients to perform productive work indicated that work capacity increased by an average of 3.3 h per patient per week [49]. At baseline, 25.7 % of respondents ($n = 202$) were on part-time absence and/or disability pension, 37.6 % were on full-time absence and/or disability pension, and 36.6 % were not on any sickness absence or disability pension. Overall, 22 % of patients increased their work capacity, 6 % decreased their work capacity and 72 % were unchanged after 1 year of treatment. Greater productivity gains were significantly correlated with shorter duration of illness ($p = 0.025$) and being employed rather than self-employed ($p = 0.041$), but did not correlate with EDSS score [49].

4.3 Long-Term Follow-Up Studies

STRATA is an ongoing, long-term (up to 10 years), open-label follow-up study of natalizumab monotherapy (300 mg intravenously every 4 weeks) in patients who have completed controlled trials, such as AFFIRM, SENTINEL or GLANCE (a phase II, 24-week, randomized trial comparing natalizumab versus placebo when added to existing glatiramer acetate therapy) and their open-label extensions, and have completed a Dosing Suspension Safety Evaluation study (neurological examination plus an MRI scan) [40, 41].

In March 2011, after 3,013 patient-years of natalizumab exposure in STRATA (median of 48 natalizumab infusions), the annualized relapse rate was 0.18 relapses/patient/year [50]. Mean EDSS scores increased in the time between completing the feeder studies and enrolment in STRATA and were 2.90 and 3.13 in natalizumab and placebo recipients, respectively, at the time of entry into STRATA [51]. Mean EDSS scores for patients who were originally treated with natalizumab or placebo prior to enrolment in STRATA were 2.70 and 3.08, respectively, at 48 weeks, and 2.85 and 3.26 at 192 weeks of treatment in STRATA [50].

In a cohort of AFFIRM patients treated for 3 years in STRATA, the annualized relapse rates were 0.079 for those who were free of disease activity after 2 years in AFFIRM ($n = 147$) and 0.162 for those not free of disease activity in AFFIRM ($n = 342$) [52]. The mean EDSS scores after 3 years of treatment with natalizumab for all patients in STRATA were significantly lower for the subset of patients who were free of disease activity in AFFIRM than in those who were not disease activity free (2.23 vs. 3.16; $p < 0.0001$) [52].

The TOP study is an ongoing, multinational, open-label, post-marketing, observational study of the long-term safety and efficacy of natalizumab treatment in natalizumab-naïve (≤ 3 doses prior to enrolment) adult patients with active

RRMS [42]. In the most recent preliminary report on the TOP study, involving 3,484 patients from 15 countries, the mean EDSS after 3 years was stable at 3.4 compared with a baseline value of 3.5 [53]. In 3,458 evaluable patients, the annualized relapse rate decreased significantly from baseline (0.28 vs. 1.98; $p < 0.0001$). Annualized relapse rates at baseline were similar (1.91–2.03) regardless of the patients' previous therapy, but after therapy for 3 years, the annualized relapse rates differed significantly ($p < 0.0001$) according to pre-enrolment therapy received by the patient: 0.16 for treatment-naïve, 0.20 for interferon, 0.23 for glatiramer acetate, 0.25 for interferon and glatiramer acetate (successively, in either order) and 0.34 for immunosuppressant [53].

5 Tolerability

The tolerability profile of natalizumab in patients with RRMS is defined to a notable extent by the occurrence of PML, a complication of therapy with natalizumab that may be fatal or result in severe disability. While the general tolerability of natalizumab in RRMS has been well defined in the phase III trials discussed in Sect. 4.1, PML has been observed only rarely in controlled trials. Therefore, PML is discussed separately in Sect. 5.3.

5.1 General Tolerability

In the phase III AFFIRM trial in which natalizumab monotherapy (300 mg intravenously every 4 weeks) [$n = 627$] was compared with placebo ($n = 315$) over 2 years, the most common treatment-emergent adverse events occurring in >10 % of patients treated with natalizumab were headache (38 %), fatigue (27 %), urinary tract infection (20 %), arthralgia (19 %), depression (19 %), lower respiratory tract infection (17 %), gastroenteritis (11 %), abdominal discomfort (11 %) and rash (11 %) [38]. The only adverse events that were significantly more frequent with natalizumab than with placebo were fatigue (27 vs. 21 %; $p = 0.048$) and allergic reactions (9 vs. 4 %; $p = 0.012$). Overall, 6 % of patients on natalizumab and 4 % on placebo discontinued therapy as a result of adverse events, and 3 and 2 %, respectively, withdrew from the study. Infections occurred in 79 % of patients in each treatment group; they were mostly mild or moderate and did not result in treatment discontinuation. Serious infections were experienced by 3.2 % of natalizumab recipients and 2.6 % of placebo recipients [38]. One case of serious cryptosporidial diarrhoea was observed in a natalizumab recipient. Infusion reactions (defined as any event occurring within 2 hours of starting the 1-h infusion) were significantly more frequent with

natalizumab than with placebo (24 vs. 18 %; $p = 0.04$), with headache being the most common event (5 vs. 3 %). Hypersensitivity reactions occurred in 4 % (25/627) of natalizumab recipients; eight (1.3 %) of these events were categorized as serious (including five cases of anaphylaxis or anaphylactoid reaction). There were five cases (<1 %) of cancer (three breast cancer, one stage 0 cervical cancer and one newly diagnosed metastatic melanoma) in the natalizumab group and one case (<1 %) of cancer (basal cell carcinoma) in the placebo group [38]. Two patients, both on natalizumab, died during the study, one of alcohol intoxication and one of malignant melanoma, although the patient had a history of malignant melanoma and had noted a new lesion at the time of the first natalizumab dose [38]. A small number of reports of melanoma occurring during treatment with natalizumab have raised the question of whether natalizumab might promote the development of melanoma. However, a meta-analysis did not show an increased risk of melanoma with natalizumab compared with placebo in clinical trials of natalizumab [54]. The results of a study on the evolution of skin melanocytic lesions in patients with MS treated with natalizumab are consistent with prevalence data and suggest that natalizumab does not promote the development of new melanomas [55].

In the phase III SENTINEL study, the only adverse events occurring significantly more often with natalizumab combined with interferon β -1a ($n = 589$) than with interferon β -1a alone ($n = 582$) were anxiety (12 vs. 8 %; $p \leq 0.01$), pharyngitis (7 vs. 4 %; $p \leq 0.05$), sinus congestion (6 vs. 3 %; $p \leq 0.01$) and peripheral oedema (5 vs. 1 %; $p \leq 0.001$) [39]. Overall, the most common adverse events (occurring with ≥ 1 % higher frequency in the combination therapy group than in the interferon β -1a alone group) were headache (46 vs. 44 %), nasopharyngitis (39 vs. 35 %), arm/leg pain (22 vs. 21 %), depression (21 vs. 18 %) and influenza-like illness (20 vs. 19 %). The incidences of infection, cancer, infusion reactions, and hypersensitivity were similar between combination therapy and interferon β -1a alone [39]. Serious infections occurred in 2.7 and 2.9 % of patients on combination therapy or interferon β -1a alone, respectively. Overall, 8 % of patients on combination therapy and 7 % taking interferon β -1a alone discontinued therapy as a result of adverse events, while 3 and 2 %, respectively, withdrew from the study due to adverse events. The incidence of serious adverse events was similar in the combination and interferon β -1a alone groups (18 vs. 21 %). There was one case of PML in a patient receiving natalizumab (see Sect. 5.3).

In line with its pharmacodynamic activity (see Sect. 2), natalizumab transiently increased the numbers of lymphocytes, monocytes, eosinophils and basophils in the peripheral blood, while neutrophil levels remained

unchanged, in both the AFFIRM and SENTINEL trials [38, 39]. Transient increases in nucleated red blood cells in peripheral blood were seen in a small number of patients in both studies.

In a pooled analysis of patients with MS treated in placebo-controlled trials, 43.5 % of natalizumab recipients ($n = 1,617$) reported adverse events compared with 39.6 % of placebo recipients ($n = 1,135$) [11]. In total, 5.8 % of natalizumab recipients and 4.8 % of placebo recipients discontinued therapy as a result of adverse events. The most commonly reported adverse events in patients treated with the recommended dose of natalizumab included dizziness, nausea, urticaria and rigors associated with infusions [11]. Adverse events occurring with an incidence ≥ 0.5 % higher with natalizumab than with placebo and classified as common ($\geq 1/100$ to $<1/10$) were urinary tract infection, nasopharyngitis, urticaria, headache, dizziness, vomiting, nausea, arthralgia, rigors, pyrexia and fatigue, while those classified as uncommon ($\geq 1/1,000$ to $<1/100$) were hypersensitivity and PML [11].

Severe drug-induced liver injury with elevations of serum transaminases and hyperbilirubinaemia have been reported for natalizumab during post-marketing surveillance [11, 56]. Some cases occurred after the first dose of natalizumab and one patient experienced recurrence after reintroduction of natalizumab [56].

5.2 Immunogenicity

By virtue of being a therapeutic protein produced by recombinant DNA technology in a murine cell line, natalizumab is prone to inducing an antibody response in treated patients, although the monoclonal antibody is humanized to limit its immunogenicity. Anti-natalizumab antibodies have been detected in variable proportions of treated MS patients, usually ranging from 4.1 to 14.1 % [38, 39, 57–62], although one recent study detected antibodies in 58 % of 73 consecutive patients, most of whom were only transiently positive (i.e., patients tested negative upon follow-up) [63].

In the AFFIRM trial, antibodies against natalizumab were detected in 9 % (57/627) of natalizumab recipients at some time during the study [38]. Persistent antibodies (detected on at least 2 occasions ≥ 42 days apart) were detected in 6 % (37/627) of patients, who displayed an increased incidence of infusion-related/hypersensitivity adverse events and a loss of natalizumab efficacy [38].

Similarly, in the SENTINEL trial, 12 % (70/589) of patients in the combination therapy group had antibodies to natalizumab and 6 % (38/589) had persistent antibodies, which resulted in a loss of efficacy and an increase in infusion-related adverse events [39].

Over 2 years in AFFIRM and SENTINEL, respectively, infusion-related reactions were experienced by 76 and 79 % of patients who were persistently positive for antibodies against natalizumab compared with 20 and 19 % of antibody-negative patients, 25 and 31 % of transiently positive patients and 18 % of placebo recipients or 20 % of interferon β -1a alone recipients [64]. In AFFIRM, hypersensitivity reactions were experienced by 46 % of persistently positive patients, 15 % of transiently positive patients and 0.7 % of antibody-negative patients; the respective proportions in SENTINEL were 21, 0 and 0.6 % [64].

In a post-marketing study in MS patients conducted in Sweden, 3.9 % (39/1,005) of natalizumab recipients had neutralizing antibodies to natalizumab detected on at least one occasion and 13 of the 27 patients who were rechecked were confirmed as positive [60]. A similar Swedish study of 1,379 MS patients treated with natalizumab between 2006 and 2011 found anti-natalizumab antibodies in 57 patients (4.1 %), of whom 20 reverted to negative status and 19 remained persistently positive; 18 patients were unconfirmed positive (i.e., had no follow-up sample) [62].

Another study in an unselected cohort of RRMS patients from four centres in different countries ($n = 4,881$) found persistent anti-natalizumab antibodies in 3.5 % of patients and transient antibodies in 1.0 % of patients [61].

Anti-natalizumab antibodies generally develop early after starting therapy, with most being detected in the first 3–4 months of therapy [59]. Studies have shown that persistently positive patients have higher titres of anti-natalizumab antibodies than transiently positive patients [57, 62], that high antibody titres are associated with low serum concentrations of natalizumab [63] and that high antibody titres and low serum natalizumab concentrations are associated with relapses and gadolinium-enhancing lesions on MRI [63].

5.3 Progressive Multifocal Leukoencephalopathy

PML is caused by opportunistic infection of the CNS with the human polyomavirus JC virus, presumably as a result of impaired immune surveillance within the CNS, following the inhibition by natalizumab of leukocyte migration across the blood–brain barrier and/or the depletion of antigen presenting cells (Sect. 2) [65, 66]. PML usually only occurs in patients with severe immunodeficiency states, such as HIV/AIDS, or in association with certain immunosuppressive agents [67]. The prevalence of anti-JC virus antibodies in MS patients was determined to be 55 % [68]. Infection of glial cells in the brain with JC virus leads to lysis of oligodendrocytes, which is the underlying pathology of PML and results in rapid nerve demyelination in subcortical white matter [66].

Only three cases of PML were recorded in pre-marketing studies of natalizumab. One case occurred in the SENTINEL study after 29 doses of natalizumab (in combination with interferon β -1a), one occurred in the open-label extension to SENTINEL after 37 doses of natalizumab and one was diagnosed post mortem in a patient treated with natalizumab (≈ 8 doses over 15 months) for Crohn's disease [39, 69]. At this time, the risk of PML associated with natalizumab was estimated to be 1 in 1,000 over a mean treatment period of 17.9 months and the benefits of treatment were considered to outweigh the risk [12]. Reports of PML associated with natalizumab therapy have continued to accumulate, such that, as of February 2012, there were 212 confirmed cases among 99,571 patients treated with natalizumab (209,123 patient-years of experience) giving an incidence of 2.1 cases per 1,000 patients (1.01 cases per 1,000 patient-years) [68]. Of the 212 patients with PML, 46 (22 %) died and 40 % (23/58) of the evaluable survivors had severe disability [68]. A recent media release in March 2013 indicates that at least 319 patients treated with natalizumab have been diagnosed with PML, 21 of whom had no clinical symptoms and had their diagnoses based entirely on MRI findings and CSF positivity for JC virus [70]. According to the manufacturer's data cited on a multiple sclerosis research website, as of 5 March 2013, there have been 343 confirmed cases of PML among >112,000 patients with MS treated with natalizumab, producing a risk of PML associated with natalizumab of 2.96 cases per 1,000 patients treated [71]. The mean duration of treatment with natalizumab at the time of PML diagnosis for these patients was ≈ 39 months [71].

The risk factors associated with PML appear to be longer duration of natalizumab therapy (particularly beyond 2 years of therapy, although data are limited beyond 4 years), prior use of immunosuppressive drugs and positivity for anti-JC virus antibodies [68]. The estimated incidence of PML in patients with all three risk factors was 11.1 cases per 1,000 patients, compared with an estimated incidence of 0.09 cases per 1,000 patients in the lowest risk subgroup (those who tested negative for anti-JC virus antibody) [68]. Therefore, testing for JC virus antibodies prior to starting natalizumab therapy and testing every 6 months thereafter to permit risk stratification is considered prudent practice [72]. An analysis of anti-JC virus antibody index values (determined by the STRATIFY JCV DxSelectTM assay) determined ≥ 6 months previously for 45 patients who developed PML compared with 1039 patients who did not develop PML found a significantly ($p < 0.0001$) higher median antibody index in PML patients compared with non-PML patients [73]. The anti-JC virus antibody index values were generally stable over at least 18 months. After stratification according to prior

immunosuppressive drug use, the significant difference between PML and non-PML patients applied only to the subset with no prior immunosuppressant use. For the latter subpopulation, anti-JC virus antibody index values >1.5 were associated with a higher risk of PML than index values ≤ 1.5 (8.1 vs. 1.2 cases per 1,000 patients at 25–48 months; 8.5 vs. 1.3 cases per 1,000 patients at 49–72 months) [73].

The incidence of PML associated with natalizumab is higher in the EU than in the US [74, 75]. In addition, the duration of natalizumab therapy beyond which the risk for PML increases significantly is longer in the US than in the EU. The reason for these differences is not known, but one theory is that it may relate to differences in body mass index. It is hypothesized that high VLA-4 receptor occupancy due to high plasma concentrations of natalizumab resulting from low body mass and/or longer treatment duration reduces immunosurveillance of the JC virus in the brain and allows PML to develop [75]. Thus, a low body mass index with a fixed dose of natalizumab may result in higher plasma concentrations of natalizumab and a higher incidence of PML. It has been suggested that increasing the interval between natalizumab infusions may reduce this risk [75].

Assessment of immune responses to JC virus by peripheral blood mononuclear cells from MS patients with natalizumab-associated PML suggests that these patients have absent or aberrant CD4⁺ T cell responses to JC virus compared with natalizumab-treated patients without PML or with healthy volunteers [76].

The increase in risk for PML with longer duration of natalizumab therapy has led to speculation that temporary interruption or termination of natalizumab treatment after approximately 2 years of therapy may be a useful strategy to reduce the risk of PML. A retrospective analysis of patients with RRMS ($n = 1,866$) in whom treatment was interrupted for ≥ 8 months indicated that annualized relapse rates and the number of gadolinium-enhancing lesions started to increase shortly after stopping natalizumab therapy and returned to pretreatment levels within 4–7 months [77]. However, in contrast to previous concerns, there was no evidence of rebound of disease activity beyond pretreatment levels. A previous small, randomized, placebo-controlled trial ($n = 72$) had suggested that relapse was more frequent after discontinuation of natalizumab (two doses administered) versus placebo (14 vs. 3 patients; $p = 0.005$) [78]. Also, a small observational study ($n = 32$) had suggested that the mean number of gadolinium-enhancing lesions observed after stopping natalizumab (≥ 12 infusions administered) was significantly higher than prior to starting natalizumab therapy in patients experiencing relapse (9.5 vs. 2.0; $p < 0.001$) [79]. In addition, an analysis of 21 patients from a single centre who

participated in the AFFIRM or SENTINEL trials suggested that the median annualized number of active T₂ lesions was increased significantly in the 15-month interval after natalizumab withdrawal compared with that observed pretreatment (10.32 vs. 3.43; $p = 0.014$) [80]. In each of these three studies, the rebound increases were mainly attributable to patients who had received a small number of natalizumab infusions prior to treatment interruption [78–80].

The pattern of disease activity recurrence upon natalizumab therapy interruption in the large retrospective analysis did not appear to be affected by the duration of natalizumab therapy and patients with more active disease had faster recurrence of more severe disease [77]. Thus, alternative treatment would be required to control disease activity upon stopping natalizumab—creating a conundrum. Since natalizumab has a half-life of 11 days, it remains in the system for some weeks after stopping treatment and its effects persist for many months [77]. Therefore, switching to an immunosuppressant soon after stopping natalizumab may place a patient at increased risk of PML and is not ideal. Also, both interferon β -1a and glatiramer acetate would presumably have already been found suboptimal before the introduction of natalizumab, thereby limiting the options for alternative treatment. Intravenous pulse monthly corticosteroid treatment during interruption of natalizumab therapy (for 90–150 days) was found to be of questionable benefit in preventing the recurrence of disease activity [81]. Therefore, some experts consider that a drug-free interval of 3–6 months is the prudent course [82].

Switching to the sphingosine 1-phosphate receptor agonist fingolimod after discontinuing natalizumab and before the recurrence of clinical disease activity has been found to be an effective exit strategy from natalizumab [83, 84]. In an uncontrolled study (published as an abstract), only two of 73 patients who switched to fingolimod after discontinuing natalizumab experienced relapse or MRI advancement, while two others experienced EDSS progression without relapse or MRI advancement [84]. In a retrospective analysis following patients for 24 weeks after discontinuing natalizumab therapy (published as an abstract), the annualized relapse rate in patients who switched to fingolimod ($n = 32$) was significantly lower than in those patients who did not receive further treatment throughout the follow-up ($n = 11$) [0.8 vs. 1.8; $p = 0.03$] [83]. The annualized relapse rate (measured from the point of stopping natalizumab) was numerically lower in patients who started on fingolimod within 12 weeks of discontinuing natalizumab ($n = 10$) than in those who started on fingolimod after 12 weeks ($n = 22$) [0.4 vs. 0.9]. While the difference was not statistically significant, it highlights the wisdom of switching before the return of substantial disease activity [83].

However, a large, multicentre, observational study in France had a less favourable experience with switching from natalizumab to fingolimod (published as an abstract) [85]. Overall, 177 of 4,500 studied patients switched after an average of 36 natalizumab infusions; 73 % of those switching were seropositive for JC virus, while 50 % were in the highest risk category for developing PML. During the washout period (duration not stated), in which 55 % were untreated and 45 % received sequential intravenous methylprednisolone treatment, 65 % of patients experienced a relapse. The duration of the washout period was the only factor predictive ($p = 0.002$) of experiencing relapse and the EDSS score had worsened at the time of starting fingolimod therapy compared with the score at the time of discontinuing natalizumab (3.7 vs. 3.6; $p = 0.004$). Of the patients who received fingolimod for ≥ 6 months, 33 % experienced at least 1 relapse and 3.3 % discontinued fingolimod for lack of efficacy or intolerance [85].

6 Pharmacoeconomic Considerations

The cost effectiveness of natalizumab therapy in the treatment of RRMS has been assessed in three fully published, modeled, cost-utility analyses performed in the US [86], the UK [87] and Sweden [88] (see Table 2). All three cost-utility analyses used Markov decision-analysis models over time horizons varying from 20 years to the patients' lifetime, with the transition states based on EDSS values. All three studies included probabilistic univariate sensitivity analyses, varying key parameters, to test the robustness of the assumptions.

The US analysis suggested that both glatiramer acetate and natalizumab were more cost effective than symptom management alone from both the healthcare system (direct costs only) and societal (including indirect costs of lost productivity) perspectives, with glatiramer acetate being dominant (more effective and less costly) over natalizumab (Table 2) [86].

In contrast, the UK analysis, performed from the societal perspective, predicted that natalizumab would be the most cost-effective disease-modifying drug, with an incremental cost-effectiveness ratio (ICER) of £2,300 per quality-adjusted life-year (QALY) gained compared with the next most costly drug, interferon- β , and an ICER of £8,200 per QALY gained compared with best supportive care, in the base-case analysis (Table 2) [87]. From a government cost perspective, the ICER for natalizumab versus interferon- β was £13,000 per QALY gained, while the ICER from the perspective of the Health and Social Services was £18,700 per QALY gained [87].

The Swedish analysis suggested that natalizumab therapy would be dominant over standard disease-modifying

drugs in use in Sweden (three interferon- β preparations and glatiramer acetate) from a societal perspective (Table 2) [88]. From a healthcare system perspective (direct costs only), the incremental cost of natalizumab therapy over standard disease-modifying drugs was predicted to be €38,145 per QALY gained [88].

The cost-utility analyses with natalizumab were generally well conducted, in that relevant costs were included, sources of data were clearly stated, clinical outcomes were relevant, appropriate discounting was applied and sensitivity analyses were conducted. However, as with all pharmacoeconomic analyses, there are study limitations. For example, even if the base-case results of cost-effectiveness analyses are robust to reasonable changes in key input variables in sensitivity analyses, they may not be applicable to other geographical regions because of differences in healthcare systems, unit costs and other factors. In addition, modelled analyses project longer-term costs and outcomes from shorter-term clinical trial data, typically using a variety of sources and extrapolating clinical trial results to the general population of interest. The selection of key studies and other data sources used to populate economic models, along with other factors such as the study perspective and specific costs included, can have an important impact on results of these analyses, particularly where differences between treatments in costs and/or utilities are small, as seen here.

7 Dosage and Administration

Natalizumab is indicated in the EU as single-agent disease-modifying therapy for the treatment of adult patients (aged ≥ 18 years) with highly active RRMS in whom a beta-interferon (recently amended to also include glatiramer acetate [13]) is inadequate or who have rapidly evolving severe disease (≥ 2 disabling relapses in 1 year and at least one gadolinium-enhancing lesion or an increase in T_2 lesion load on brain MRI) [11]. Concomitant administration of natalizumab with interferon- β or glatiramer acetate is contraindicated. Concurrent use of immunosuppressants may increase the risk of infections, including opportunistic infections and is contraindicated [11].

The recommended dosage is 300 mg (15 mL of concentrate added to 100 mL of normal saline) by intravenous infusion over ≈ 1 h (≈ 2 mL/min) once every 4 weeks for up to 2 years, at which point the benefit-risk ratio should be reassessed, particularly with regard to risk factors for PML (duration of therapy, prior immunosuppressant use and positivity for anti-JC virus antibodies), before continuing therapy with natalizumab [11]. If patients have received prior immunosuppressive agents (e.g., mitoxantrone, cyclophosphamide and azathioprine), physicians must

Table 2 Cost-utility analyses of natalizumab in the treatment of patients with relapsing-remitting multiple sclerosis

	Earnshaw et al. [86]	Gani et al. [87]	Kobelt et al. [88]
Country	US	UK	Sweden
Analysis design	Markov model	Markov model	Markov model
Time horizon	Lifetime	30 years	20 years
Comparator(s)	GA and BSC	INF β , GA and BSC	Standard DMDs (INF β and GA)
Clinical data source(s)	Pivotal clinical trials and published data	Pivotal clinical trials (NAT and GA), meta-analysis (INF β) and UK MS Medical Resource Utilisation Survey	Pivotal clinical trial (NAT) and Stockholm MS Registry (DMDs)
Perspective	Healthcare system and societal	Societal	Societal
Year of costing	2007	2006	2005
Discounting (annual rate)	3 % (costs and outcomes)	3.5 % (costs and outcomes)	3 % (costs and outcomes)
Cost ($\times 1,000$)	Healthcare: NAT \$US422.21, GA \$US408.00 and BSC \$US341.44 Societal: NAT \$US1,130.69, GA \$US1,106.22 and BSC \$US1,162.54	NAT £449.5, INF β £445.2, GA £444.8 and BSC £427.1	NAT €609.85 and DMDs €613.68
QALYs gained	NAT 9.271, GA 9.272 and BSC 9.137	NAT 7.4, INF β 5.5, GA 5.1 and BSC 4.7	NAT 9.33 and DMDs 8.99
ICER	Healthcare: NAT \$US606,228 vs. BSC and GA \$US496,222 vs. BSC; GA dominant vs. NAT Societal: both NAT and GA dominant vs. BSC; GA dominant vs. NAT	NAT £2,300 vs. INF β , £2,000 vs. GA and £8,200 vs. BSC	NAT dominant vs. DMDs

BSC best supportive care (also referred to as ‘symptom management alone’ [86]), DMDs disease-modifying drugs, GA glatiramer acetate, ICER incremental cost-effectiveness ratio (incremental cost per additional QALY gained over the comparator), INF β interferon- β , MS multiple sclerosis, NAT natalizumab, QALYs quality-adjusted life-years

ensure that they are not immunocompromised before initiating natalizumab therapy [11]. Patients should be observed during infusion and for up to 1 h after infusion for signs and symptoms of hypersensitivity reactions to natalizumab.

Natalizumab is not recommended for use in patients aged >65 years, since there is no clinical experience with this patient population. The efficacy and safety of natalizumab have not been established in paediatric patients; therefore, natalizumab is contraindicated in children and adolescents [11]. The safety of natalizumab during pregnancy has not been established; it should not be used during pregnancy unless considered necessary [11]. Natalizumab has not shown any evidence of teratogenicity or increased risk of pregnancy loss in patients with MS [89, 90], but has shown reproductive toxicity at supra-therapeutic doses in some animal studies [11, 90]. Natalizumab is currently listed as FDA pregnancy category C along with interferon- β and fingolimod, whereas glatiramer acetate is category B and mitoxantrone is category D [90]. While dose adjustment is unlikely to be required in patients with

renal or hepatic impairment, natalizumab has not been assessed in these patients [11].

Local prescribing information should be consulted for detailed information, including contraindications, precautions and use in special patient populations.

8 Place of Natalizumab in the Management of Relapsing-Remitting Multiple Sclerosis

Current treatment guidelines, although somewhat outdated, generally recommend the disease-modifying drugs interferon- β or glatiramer acetate for first-line treatment of RRMS [8, 91–93]. It is recommended that treatment with disease-modifying drugs be started early in the disease process, including in patients with the initial CIS [92, 93], since, in these individuals, interferon- β reduced the conversion rate to MS from 40–50 % in untreated patients to 28–35 % over a period of 2–3 years [92]. However, the efficacy of these agents in RRMS is limited in that they reduce the annualized relapse rate by ≈ 30 % over 2 years

of treatment [2]. Approximately two-thirds of patients display breakthrough disease (i.e., clinical or imaging evidence of disease activity, despite treatment with a disease-modifying drug) within 2 years of beginning therapy with interferon- β or glatiramer acetate [94]. Corticosteroids, such as methylprednisolone, are useful in reducing the duration of relapses, but do not appear to have any significant effects on long-term functional improvement or relapse occurrence [91]. Linoleic acid may reduce the progression of disability, but appears to be effective only in patients with low disability (EDSS ≤ 2) [91]. Cytotoxic and immunosuppressive agents have been widely used, although evidence of long-term benefit in modifying the course of the disease has been inconsistent or conflicting for many. The UK treatment guidelines recommend that cyclophosphamide, cladribine, long-term corticosteroids, linomide, hyperbaric oxygen, antiviral agents and myelin basic protein should not be used, since there is insufficient research evidence of beneficial effects on the course of MS [91]. These guidelines also recommend that azathioprine, mitoxantrone, intravenous immunoglobulin, plasma exchange and intermittent short-course high-dose methylprednisolone should only be used by experts after full discussion of the risks and in a formal evaluation setting with close monitoring for adverse effects [91]. The anti-inflammatory agent sulfasalazine does not appear to provide therapeutic benefit in MS, while the immunosuppressive agents cyclosporin and methotrexate have provided conflicting results [8, 91].

Natalizumab, the first targeted disease-modifying therapy for RRMS, is approved in the EU as single-agent therapy in patients refractory to interferon- β or in patients with severe, rapidly evolving disease (Sect. 7). These restrictions on its use relate to concerns over the relatively rare, but potentially fatal, complication PML. Single-agent therapy was stipulated since the original cases of PML occurred in patients who were treated concomitantly with interferon- β or had been heavily pretreated. However, PML has since been observed most often in patients receiving natalizumab monotherapy (Sect. 5.3).

Another targeted therapy, the orally administered sphingosine 1-phosphate receptor agonist fingolimod, is also approved for the treatment of RRMS [95]. Fingolimod, at the recommended dosage of 0.5 mg/day, reduced the annualized relapse rate over 1–2 years by 54 % compared with placebo and 52 % compared with intramuscular interferon β -1a [96, 97]. Fingolimod also reduced the risk of disability progression, confirmed at 3 months, by 30 % compared with placebo [96], but did not differ significantly from interferon β -1a for this endpoint [97]. In the EU, fingolimod, like natalizumab, is approved as single-agent disease-modifying therapy in patients refractory to interferon- β or in patients with severe, rapidly evolving RRMS

[98]. This restriction of fingolimod use to those patients with greater need is related to tolerability concerns, particularly unexplained death and serious cardiovascular events shortly after starting therapy [99].

There are a number of new drugs in late-phase clinical development for MS that have demonstrated promising activity [100]. Oral dimethyl fumarate (BG-12), administered two or three times daily, was shown in phase III trials to reduce the annualized relapse rate by ≈ 50 % compared with placebo and to reduce the risk of disability progression by 34–38 % compared with placebo in one of these trials (the reduction in risk was not significant in the other trial) [101, 102]. Dimethyl fumarate is registered in the US and has received a positive opinion from the European Medicines Agency, recommending the granting of a marketing authorization for RRMS in the EU [103]. Another oral drug, teriflunomide, the active metabolite of leflunomide, is marketed in the US and has also received a positive opinion from the European Medicines Agency, recommending the granting of a marketing authorization for RRMS in the EU [104]. In phase III clinical trials, teriflunomide reduced the annualized relapse rate by 31–36 % compared with placebo and reduced the risk of sustained progression of disability by 26–32 % at a dosage of 14 mg once daily [100, 105]. The oral agent laquinimod [106, 107] and the monoclonal antibody alemtuzumab are both at the preregistration stage of clinical development. In a phase III trial, laquinimod reduced the annualized relapse rate by 23 % compared with placebo [106], but in a second placebo-controlled, phase III trial the reduction was not statistically significant [107]. In the two trials, laquinimod reduced the risk of disability progression by 36 and 34 %, respectively, compared with placebo. In two active-comparator, phase III trials, alemtuzumab was shown to reduce the annualized relapse rate by 50 and 54 %, respectively, and the risk of sustained accumulation of disability over 6 months by 42 and 30 %, respectively, compared with interferon β -1a [108, 109]. The monoclonal antibodies daclizumab (with a modified glycosylation profile) and ocrelizumab are both in phase III development. Compared with placebo, daclizumab produced reductions of 50–54 % in annualized relapse rate and 43–57 % in the risk of disability progression at 52 weeks in a phase III trial [110]. Ocrelizumab has only been assessed in phase II trials, but has demonstrated high-level reductions (73–80 % vs. placebo) in annualized relapse rate [111]. How these emerging agents compare with natalizumab and fingolimod in the treatment of RRMS is uncertain, since none have been compared in randomized controlled trials.

Natalizumab binds VLA-4 and acts as a selective adhesion molecule antagonist. It is believed to be of benefit in RRMS predominantly by preventing the translocation of activated leukocytes across the blood–brain barrier into the

CNS and also by limiting the migration of leukocytes within the CNS (Sect. 2). This is supported by studies showing that natalizumab treatment in patients with MS reduced the number of T cells, B cells, plasma cells and dendritic cells in the CNS (Sect. 2). During treatment with natalizumab, the numbers of lymphocytes, monocytes, eosinophils and basophils, but not neutrophils (which do not express VLA-4), in the peripheral blood were transiently increased (Sect. 5.1), indicating retention of these leukocytes in the systemic circulation. The activity of T cells in the peripheral blood was not suppressed, but even appeared to be stimulated with respect to production of pro-inflammatory cytokines (Sect. 2). Upon natalizumab treatment interruption/termination, the levels of serum VLA-4, soluble VCAM and circulating leukocytes returned to baseline levels by 4 months and paralleled a return of disease activity as assessed by brain imaging (Sect. 2).

In the pivotal AFFIRM trial, natalizumab monotherapy reduced the annualized relapse rate by 68 % at 1–2 years compared with placebo (Sect. 4.1). Although indirect comparisons are flawed and need to be viewed with caution, natalizumab does appear to be more efficacious than interferon- β and glatiramer acetate, and at least as effective as fingolimod in reducing annualized relapse rates. Unfortunately, natalizumab has not been directly compared with any of these agents in controlled trials.

Natalizumab also significantly reduced the risk of sustained progression of disability compared with placebo (Sect. 4.1). Treatment with natalizumab monotherapy significantly reduced the numbers of T₂-hyperintense lesions, gadolinium-enhancing lesions, new T₁-hypointense lesions and new non-enhancing T₁-hypointense lesions at 1–2 years compared with placebo, as well as significantly reducing both T₂-hyperintense and T₁-hypointense lesion volumes (Sect. 4.1.1). Overall, natalizumab monotherapy eliminated all clinical and radiological evidence of disease at 2 years in a significant proportion of patients compared with placebo (Sect. 4.1.1).

Long-term, open-label treatment with natalizumab for up to 192 weeks maintained a low mean annualized relapse rate and a low mean EDSS score throughout treatment (Sect. 4.3). The extent of response to natalizumab seen in controlled trials varies between patients and these differences in response appear to be generally maintained over long-term treatment (Sect. 4.3). In patients receiving long-term, open-label natalizumab in clinical practice, annualized relapse rates after 3 years differed significantly depending upon their previous pre-enrolment therapy, being lowest when previously untreated and highest when following immunosuppressants (Sect. 4.3).

The natural course of MS is variable, with innate improvements in disability over 1 or 2 years not unusual [112], but patients eventually suffer increased disability,

resulting either from incomplete recovery from relapses or, more importantly, the onset of progressive disease after many years [2, 6, 7]. Patients with RRMS have reduced HR-QOL compared with the general population norm (Sect. 4.2.1). Clinical improvement during natalizumab monotherapy in the AFFIRM trial was associated with improved HR-QOL from 24 weeks (i.e., the first assessment) onwards, with both SF-36 summary scores and six of eight SF-36 items being significantly improved compared with placebo at 2 years (Sect. 4.2.1). With regard to clinically important improvements from baseline to 2 years, those for PCS, but not those for MCS, were statistically significant. In real-world clinical practice, almost half of all patients reported improved overall HR-QOL after only three infusions of natalizumab and >80 % reported improvement in at least one physical item of the MSIS-29 questionnaire (Sect. 4.2.2). The improvements in physical functioning were supported by a Swedish survey, which found that 22 % of those treated with natalizumab for 1 year were able to increase their capacity to perform productive work (Sect. 4.2.2).

Natalizumab was generally well tolerated in patients with RRMS participating in clinical trials, with headache, fatigue, urinary tract infection, arthralgia, depression and lower respiratory tract infection being the most common treatment-emergent adverse events during monotherapy in the AFFIRM trial (Sect. 5.1). When administered in combination with interferon β -1a, the adverse events observed with natalizumab were similar to those with interferon β -1a alone; in particular, the incidences of cancer, infections, hypersensitivity and infusion reactions were similar. Concerns that natalizumab therapy might increase the incidence of malignant melanoma appear to be unfounded (Sect. 5.1). Opportunistic infections (other than PML) have been observed during natalizumab therapy, for example with Herpes simplex or Varicella zoster, although the only noted serious opportunistic infection with natalizumab in clinical trials in patients with MS was a case of cryptosporidial diarrhoea in the AFFIRM trial (Sect. 5.1).

Although natalizumab is a humanized monoclonal antibody, it retains a certain level of immunogenicity. Approximately 6 % of natalizumab recipients in the AFFIRM and SENTINEL trials had persistent antibodies to natalizumab that resulted in loss of efficacy of natalizumab and an increase in infusion reactions, particularly hypersensitivity reactions (Sect. 5.2). Patients who were transiently positive for antibodies against natalizumab experienced lower incidences of hypersensitivity reactions than those who were persistently positive. Data from a large observational study suggest that the incidence of patients who develop persistent neutralizing antibodies to natalizumab during therapy in normal clinical practice is about 3.5 % (Sect. 5.2).

PML is an uncommon complication of treatment with natalizumab, but the total number of cases continues to increase despite recognition of the major risk factors, which consist of longer duration of natalizumab treatment (particularly >2 years), prior use of immunosuppressive drugs and presence of anti-JC virus antibodies (Sect. 5.3). PML is the primary limiting factor in the use of natalizumab and is a consequence of natalizumab's pharmacodynamic activity, which is believed to result in impaired immune surveillance in the CNS, allowing opportunistic infection of glial cells with the JC virus, possibly involving reactivation of latent infection. The 22 % fatality rate associated with natalizumab-induced PML and the 40 % incidence of severe disability in survivors of PML make avoidance and management of this complication priorities in natalizumab therapy. Plasma exchange was effective in removing natalizumab from plasma following treatment termination (Sect. 3), supporting its use to aid more rapid immune reconstitution and earlier manifestation of immune reconstitution inflammatory syndrome in patients developing signs of PML. It is hoped that risk stratification, anti-JC antibody monitoring, improved surveillance and limitation of treatment duration (or treatment interruption), along with prompt treatment will limit the impact of PML.

MS incurs considerable costs from both the healthcare system and societal perspectives [113]. Therefore, pharmacoeconomic considerations play an important role in determining the choice of pharmacotherapy for MS. Cost-utility analyses performed in the UK and Sweden each found natalizumab to be more cost effective than other disease-modifying drugs (interferon- β or glatiramer acetate) or best supportive care from a societal perspective, which includes the cost of lost productivity (Sect. 6). Natalizumab was dominant (more effective and less costly) in the Swedish analysis and had ICERs in the region of £2,000 per QALY gained compared with interferon- β and glatiramer acetate in the UK analysis—values well within commonly accepted willingness-to-pay thresholds for cost effectiveness. In contrast, a US analysis found glatiramer acetate to be dominant over natalizumab from both a healthcare and societal perspective, although the additional clinical benefit with glatiramer acetate was slight. The incremental costs per QALY for natalizumab (\$US606,228) and glatiramer acetate (\$US496,222) compared with symptom management alone from the healthcare perspective were well outside the commonly accepted willingness-to-pay threshold (e.g., \$US50,000). However, from a societal perspective, both natalizumab and glatiramer acetate were dominant over symptom management alone (Sect. 6).

In conclusion, natalizumab is the first targeted disease-modifying drug to be approved for the treatment of RRMS. In the EU it is approved for use as single disease-modifying therapy in adult patients with RRMS refractory to interferon-

β or glatiramer acetate, or in patients with rapidly evolving, severe RRMS. In a well-controlled clinical trial in patients with RRMS, natalizumab 300 mg intravenously every 4 weeks for 2 years significantly reduced the annualized relapse rate compared with placebo, significantly reduced the risk of sustained progression of disability and significantly reduced the numbers of T₂-hyperintense, gadolinium-enhancing and T₁-hypointense lesions, as well as lesion volumes, on MRI. Improvements in annualized relapse rates and EDSS scores were maintained during long-term therapy. Patients treated with natalizumab generally experienced significantly improved HR-QOL, particularly for the physical components. Natalizumab was generally well tolerated, with only fatigue and allergic reactions being more frequent than with placebo. A small proportion of patients developed persistent neutralizing antibodies against natalizumab. While only two cases of PML were observed during clinical trials or their immediate extensions in patients with MS, the total number of cases continues to increase. The overall post-marketing incidence of PML remains low, although further clinical experience is required to fully assess the long-term safety profile in different risk categories. Pharmacoeconomic analyses generally found natalizumab to be cost effective from a societal perspective, which incorporates the cost of lost productivity. Therefore, as long as the risk of PML is managed effectively, natalizumab is a valuable therapeutic option for adults with highly active relapsing forms of MS.

Data selection sources: Relevant medical literature (including published and unpublished data) on natalizumab was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 10 July 2013], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.

Search terms: Natalizumab, multiple sclerosis, multiple sclerosis relapsing-remitting, relapsing-remitting multiple sclerosis, JC virus.

Study selection: Studies in patients with relapsing-remitting multiple sclerosis who received natalizumab. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Disclosure The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made by the author on the basis of scientific and editorial merit.

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