Physician* Information and Management Guidelines for Patients With Multiple Sclerosis Receiving TYSABRI (IV & SC) Therapy (NATALIZUMAB)

Version 19: February 2021

***TYSABRI therapy is to be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions**

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LIST OF ABBREVIATIONS

Abbreviation	Definition
2D	2 dimensional
3D	3 dimensional
ADC	Apparent diffusion coefficient
CD	Crohn's disease
CSF	Cerebrospinal fluid
CI	Confidence interval
CNS	Central nervous system
DNA	Deoxyribonucleic acid
DWI	Diffusion weighted imaging
EID	Extended interval dosing
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FSW	Fast spin echo
FLAIR	Fluid-attenuated inversion recovery
GCN	Granule cell neuronopathy
Gd	Gadolinium
HCP	Healthcare Professional
IA	Immunoadsorption
Ig	Immunoglobulin
IVIg	Intravenous immunoglobulin
IRIS	Immune Reconstitution Inflammatory Syndrome
IS	Immunosuppressant
JCV	John Cunningham virus
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
PAC	Patient alert card
PL	Package leaflet
PD	Pharmacodynamic
PK	Pharmacokinetic
PLEX	Plasmapheresis / plasma exchange
PML	Progressive multifocal leukoencephalopathy
Q4W	Once every 4 weeks
Q6W	Once every 6 weeks
SID	Standard interval dosing

Abbreviation	Definition
SmPC	Summary of Product Characteristics
STRATA	Safety of Tysabri Re-dosing and Treatment
$t_{1/2}$	Elimination half-life
TYGRIS	Tysabri Global Observational Program in Safety
TOP	Tysabri Observational Programme
TOUCH	Tysabri Outreach: United Commitment to Health
US	United States

1. INTRODUCTION

This guidance document has been developed for those physicians initiating and supervising patient treatment with TYSABRI® (natalizumab) in accordance with the conditions of the Marketing Authorisations of the drug, in order to ensure its safe and effective use. It contains information to be used in conjunction with the TYSABRI Summary of Product Characteristics (SmPC) (Appendix 1) and is supported by the Treatment Initiation Form, Treatment Continuation Form, and Treatment Discontinuation Form (Appendix 4). This guidance provides additional risk mitigation measures; for primary guidance, please see the SmPC.

The physician pack also includes a copy of the Package Leaflet (PL) and Patient Alert Card (Appendix 2 and Appendix 3).

It is recommended that physicians initiating and supervising treatment with natalizumab should share relevant sections of this document with radiologists who are involved in the differential diagnosis of progressive multifocal leukoencephalopathy (PML).

The guidance document focuses primarily on PML, which currently remains the most important adverse reaction affecting patients treated with natalizumab.

2. PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Prescribers should be aware that opportunistic infections, including PML, may occur during natalizumab therapy. An opportunistic infection is an infection due to an organism that generally does not cause disease or that causes only mild or self-limited disease, for example, oesophageal candidiasis, mycobacterial infections, and disseminated viral infections.

Cases of PML have been reported in patients during natalizumab treatment and up to 6 months after the last dose of natalizumab. Patients and their caregivers need to be advised of symptoms that may be indicative of early PML and continue to be vigilant through the treatment duration and 6 months after discontinuation (see Section 3.2, Appendix 3, and Appendix 4).

If an opportunistic infection is suspected, dosing with natalizumab must be suspended until it can be excluded through further evaluations.

2.1. Aetiology and Epidemiology

PML is a subacute, evolving infectious disease of the CNS caused by John Cunningham virus (JCV). Cases have also been reported as a consequence of immunosuppressant (IS) treatment of patients with autoimmune disorders and solid organ transplant recipients.

PML affects the subcortical white matter and is caused by the reactivation of JCV, a human polyomavirus [Wollebo 2015]. Initial infection with JCV is thought to occur during childhood, after which the virus persists primarily in the kidneys. Infection with the archetypal virus does not cause disease. However, mutations in the noncoding region and then the capsid protein-coding region of the viral deoxyribonucleic acid (DNA) are thought to lead to a pathogenic form that can enter the brain and infect the CNS. When coupled with a compromised immune system, reactivation of this neurotropic virus can occur, resulting in PML.

A seroprevalence study utilising the serum anti-JCV antibody assay (STRATIFY JCV) in over 6000 patients with MS demonstrated the prevalence of anti-JCV antibodies to be approximately 55%. Anti-JCV antibody prevalence in the EU was reported as ranging from 48.8% to 69.5% in the EU in a cross sectional study of MA patients irrespective of treatment. In the MS population, anti-JCV antibody prevalence increased with age and was lower in women than in men in all cohorts tested. In general, anti-JCV antibody prevalence did not appear to be affected by prior immunosuppressant use, prior exposure to Tysabri, or duration of Tysabri exposure.

2.2. Pathology

Replication of JCV in the brain causes a lytic infection of oligodendrocytes resulting in the widespread destruction of myelin. Microscopic lesions develop in the subcortical white matter, which enlarge and may coalesce with a characteristic pattern on magnetic resonance imaging (MRI) examination.

Besides oligodendrocytes, JCV can also infect cerebellar granule cell neurons, resulting in JCV granule cell neuronopathy (GCN). JCV GCN is associated with mutations in the C-terminus of the JCV VP1 gene, coding for the major capsid protein. JCV GCN can

occur in isolation or in combination with PML. There have been very rare reports of JCV GCN in patients receiving natalizumab [Agnihotri 2014; Schippling 2013].

2.3. PML in Natalizumab-Treated Patients

During extended pivitol trials, two cases of PML were reported in MS patients and a full safety evaluation revealed one further case in a clinical trial patient with Crohn's disease. In the postmarketing setting, the risk of PML has been well characterized over the first 6 years of treatment with the identification of different levels of PML risk in different patient subgroups.

2.4. PML Risk Factors

All data available to characterise PML risk are from the IV route of administration. Considering the similar PD profiles, the same PML risk and relevant risk factors are assumed for the different routes of administration. The following risk factors have been associated with the development of PML during natalizumab therapy:

- **The presence of anti-JCV antibodies in blood or serum.** Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared with patients who are anti-JCV antibody negative. However, PML only occurs in a minority of patients who are anti-JCV positive because JCV infection is only one of several steps required for the development of PML. The anti-JCV antibody assay is of greatest utility in stratifying PML risk when a positive test result is used in combination with the other identified risk factors described below.
- **Treatment duration**. The risk of PML increases with natalizumab therapy duration, especially beyond 2 years.
- **Prior immunosuppressant therapy**. Patients who have a history of treatment with an IS prior to starting natalizumab are also at increased risk of developing PML.

Patients who have all 3 risk factors for PML (i.e., are anti-JCV antibody positive, have received more than 2 years of natalizumab therapy, and have received prior IS therapy) have a higher risk of PML. In anti-JCV antibody-positive, natalizumab-treated patients who have not used prior IS therapies, the level of anti-JCV antibody response (index) is associated with the level of risk for PML (i.e., the risk is greater in those with a high antibody index compared with those with a low index). Currently available evidence suggests that the risk of PML is low at an index less than or equal to 0.9 and increases substantially above 1.5 for patients who have been receiving treatment with natalizumab for longer than 2 years [Ho 2017].

Irrespective of the presence or absence of PML risk factors, heightened clinical vigilance for PML should be maintained in all patients treated with natalizumab and for 6 months after discontinuation of therapy.

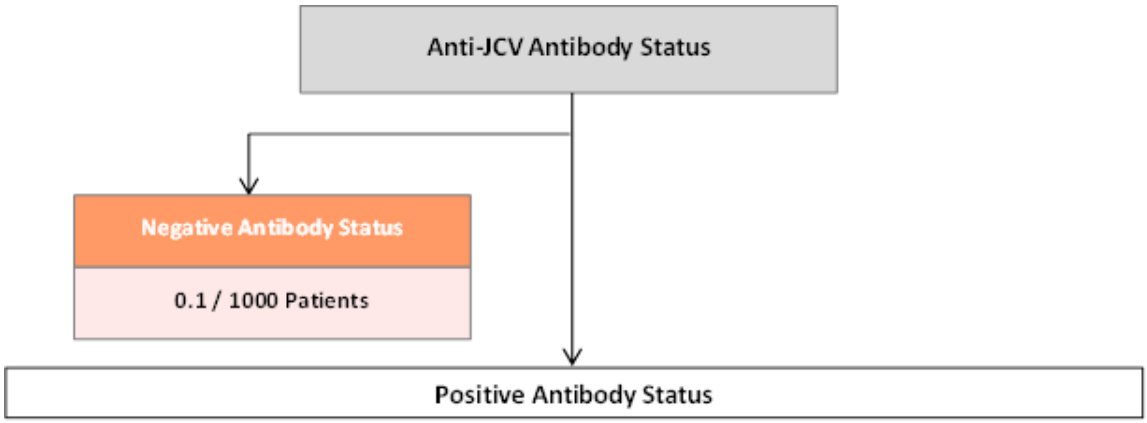
The PML Risk Estimates Algorithm (Figure 1) summarises PML risk by anti-JCV antibody status, prior IS use, and duration of natalizumab therapy (by year of treatment) and stratifies this risk by index value when applicable.

- *For anti-JCV antibody-negative patients:* PML risk estimates are based on data from approximately 125,000 natalizumab-exposed patients where the estimated incidence of PML for anti-JCV antibody-negative patients is

0.1/1000. Anti-JCV antibody-negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status, or a false-negative test result.

- *For anti-JCV antibody-positive patients:* Risk estimates were derived using the Life Table Method based on the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical trials. The risk estimates from the Life Table Method are forward-looking in yearly intervals: for example, the risk estimate corresponding to the 25- to 36-month natalizumab exposure period is the PML risk estimated for the following year in patients treated with natalizumab for 24 months. The individual treatment length of each patient takes drop-outs into account (e.g., treatment discontinuation). A higher anti JCV antibody index is associated with an increased risk of PML.
- *For anti-JCV antibody-positive patients who have used IS previously*: These patients are at an increased risk of PML because prior IS use is recognised as an independent risk factor for PML. PML risk estimates for this patient population are based on natalizumab clinical trial data where prior IS use comprised the following 5 IS therapies: mitoxantrone, methotrexate, azathioprine, cyclophosphamide, and mycophenolate mofetil. The exact mechanism by which prior use of these 5 IS therapies lead to an increased PML risk during natalizumab treatment is unknown. In patients with prior IS, current data do not show an association between higher index and PML risk. The underlying biological explanation for this effect is unknown. Further stratification of PML risk by anti-JCV antibody index interval for patients with no prior use of IS was derived from combining the overall yearly risk with the antibody index distribution.

Figure 1: PML Risk Estimates Algorithm

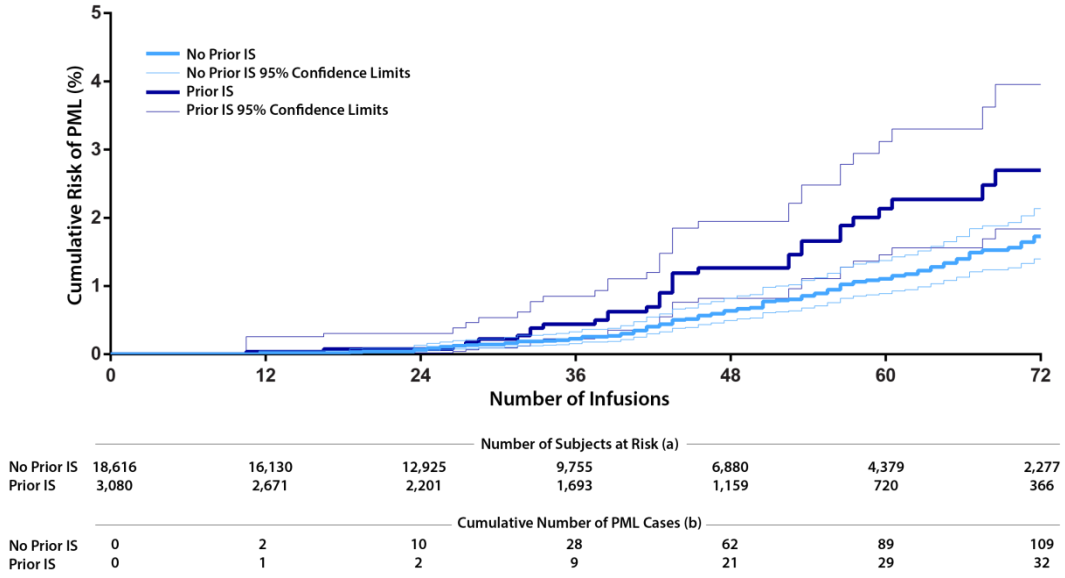


Natalizumab Exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with Prior IS use
	No index value	Antibody Index ≤ 0.9	Antibody Index > 0.9 ≤ 1.5	Antibody Index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
37-48 months	4	0.4	2	7	8
49-60 months	5	0.5	2	8	8
61-72 months	6	0.6	3	10	6

IS = immunosuppressant; JCV = John Cunningham virus; PML = progressive multifocal leukoencephalopathy.
Exposure is shown up to 72 months only as data beyond 6 years of treatment are scarce.

Additionally, some physicians may find a Kaplan-Meier (KM) curve useful to provide a visual representation of cumulative PML risk over time using a time-to-event analysis (Figure 2). In the KM curve, PML risk estimates for a given timepoint represent the total cumulative risk up to that timepoint (for example, at the timepoint of 48 months, the risk estimate on the KM curve represents the total risk up to 48 months, not the risk between 24 months and 48 months). Like Figure 1, data for these analyses were also obtained from the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical trials and also takes into account the individual treatment length of each patient with consideration of drop-outs (e.g., treatment discontinuation).

Figure 2: Cumulative PML Risk Over Time for Anti-JCV Antibody-Positive Patients Stratified by Prior IS



	Number of Subjects at Risk (a)						
No Prior IS	18,616	16,130	12,925	9,755	6,880	4,379	2,277
Prior IS	3,080	2,671	2,201	1,693	1,159	720	366
	Cumulative Number of PML Cases (b)						
No Prior IS	0	2	10	28	62	89	109
Prior IS	0	1	2	9	21	29	32

IS = immunosuppressant; JCV = John Cunningham virus; PML = progressive multifocal leukoencephalopathy.
Note: number of PML cases after 72 infusions: No Prior IS = 11, Prior IS = 4.
For patients with missing data on anti-JCV antibody status and/or prior IS use, multiple imputation methodology is used to impute the status. (a) Average number of subjects who were in the study and did not have the event at the end of the specified time over multiple imputations. (b) Cumulative number of PML cases at the end of the specified time.
Source: TYSABRIMS/PRAC-ART20/POOLED/F-TTPML-KM-PRIORIS-MI5-V2-SAS

2.5. Extending the Dosing Interval for PML Risk Mitigation

It should be noted that the standard interval dosing (SID) for natalizumab is 300 mg administered once every 4 weeks (Q4W).

The analysis of US anti-JCV antibody-positive natalizumab patients (TOUCH registry) supports that there is a significant reduction in the risk of associated PML in anti-JCV antibody-positive patients treated with an average natalizumab dosing interval of approximately 6 weeks (Q6W), so-called extended interval dosing (EID), compared with the approved dosing regimen, which is every 4 weeks (refer to the SmPC Section 5.1 [Pharmacodynamic effects]). In accordance with SmPC Section 4.4 (Special warnings and precautions for use), caution is required if extending the dosing interval of natalizumab as no prospective randomised controlled clinical trials have been completed to evaluate the efficacy of Q6W dosing, and the benefit/risk ratio for any dosing interval other than Q4W has not been established. The efficacy, tolerability, and safety of extending the dosing interval to every 6 weeks in patients who are stable on 4-weekly dosing for ≥ 1 year is currently being studied in a prospective, randomised, controlled clinical trial (NOVA Study 101MS329, https://clinicaltrials.gov, NCT03689972).

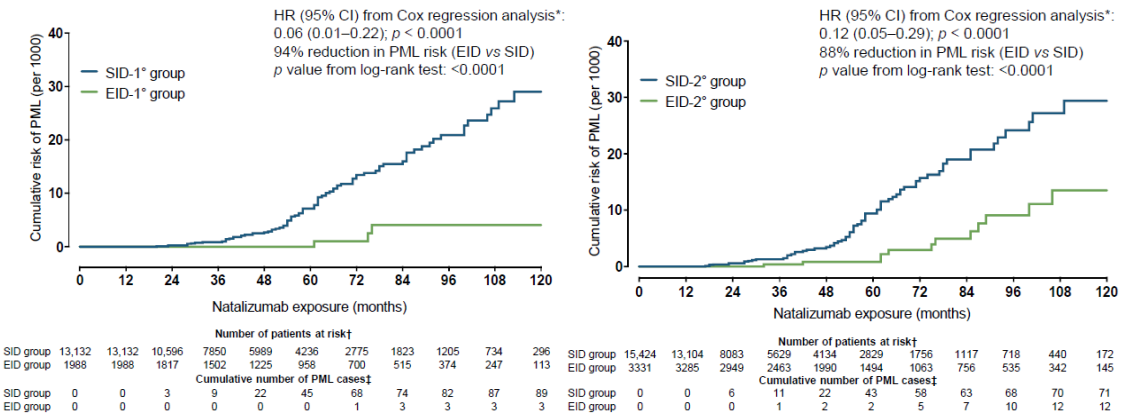
All information available to date on EID efficacy and safety come from evaluation of the IV route of administration. There are no data available on either the safety or efficacy of EID with SC route of administration and thus neither the benefits nor risks of EID SC has been established.

Summary results from real-world data on extended interval dosing

In 2017, a prespecified, retrospective analysis of anti-JCV antibody-positive patients receiving natalizumab in the United States (US) was conducted to compare the risk of PML between patients who received SID and those who received EID. Three distinct analyses of EID versus standard interval dosing were performed. Each analysis represented a different real-world clinical practice scenario of extending the interval between doses. The analyses used different inclusion criteria (definitions) for patients on EID based on the number of doses received during specified time periods to test different hypotheses about the potential effect of EID on PML risk [Ryerson 2019]. EID PML cases were only observed for the primary and secondary definitions.

The primary definition identified EID based on the last 18 months of natalizumab exposure. Analyses showed that the majority of EID patients had received SID during the first 18 months of natalizumab exposure. In the last 18 months of natalizumab treatment the median number of doses received by EID patients was 13 or approximately one dose every 42 days (6 weeks). The secondary definition identified EID periods of ≥ 6 months occurring at any time during the treatment history with the majority of patients included having switched to EID after > 1 year of the SID (median 25 infusions). KM estimates of time to PML and the probability of developing PML for EID versus SID are presented in Figure 3. The analyses concluded that EID treatment after a period of SID treatment is associated with a lower risk of PML than SID treatment in anti-JCV antibody-positive patients. Efficacy data were not available within this dataset, preventing any conclusions on EID benefit/risk. Even though the risk of PML in EID patients may be lower according to this analysis, patients treated with EID should receive monitoring for PML following the same guidance as that provided for patients treated in accordance with SID.

Figure 3: Kaplan-Meier Estimates of the Cumulative Risk of PML for Primary (A) and Secondary (B) EID Analyses



CI = confidence interval; EID = extended interval dosing; HR = hazard ratio; PML = progressive multifocal leukoencephalopathy; SID = standard interval dosing.
*EID versus SID Cox model includes age, sex, prior use of immunosuppressant therapy, EID/SID group, and calendar year at the start of natalizumab therapy as covariates.
†Number of patients who were still in the study and did not have PML at the end of the specified time.
‡Cumulative number of PML cases at the end of the specified time.

Results from efficacy modelling data

Models of pharmacokinetics (PK), pharmacodynamics (PD), and efficacy from clinical trial data developed by Biogen suggest that the efficacy of Q6W dosing is comparable to that of SID in patients who were switched to EID after ≥ 1 year of SID treatment [Chang 2020]. Consistently, publications reported that treatment with longer dosing intervals in clinical practice had similar effectiveness in patients who initially received Q4W dosing and subsequently switched to longer dosing intervals [Bomprezzi and Pawate 2014; Yamout 2018; Zhovtis Ryerson 2019]. PK/PD/efficacy models using data (n = 175) from RESTORE [Fox 2014], which included only patients who had ≥ 1 year of SID treatment without relapse in the prior year, were developed to explore the risk of MS relapse for patients with different body weights (40-59 kg, 60-79 kg, 80-99 kg, 100-120 kg) and dosing intervals (Q5W, Q6W, Q7W, and Q8W). The models suggest that the risk of return of MS disease activity for patients switching to longer dosing intervals increases with length of dosing interval (especially ≥ 7 weeks) and body weight (especially ≥ 80 kg) [Chang 2020]. No prospective studies have been completed to validate these models. It is recommended that physicians monitor any patients who switch to longer dosing intervals, and particularly those patients with higher body weight (≥ 80 kg), for potential signs of return of MS disease activity. Previous exposure/response models [Muralidharan 2017] suggested that efficacy would be lower if patients initiated natalizumab with dosing other than 300 mg Q4W, but these models do not represent outcomes associated with initiating natalizumab as Q4W dosing and later switching to longer dosing intervals.

2.6. Recommended Patient Monitoring

2.6.1. Testing for Anti-JCV Antibodies

Testing serum for anti-JCV antibodies provides supportive information for risk stratification of natalizumab therapy. Testing for serum anti-JCV antibodies prior to initiating natalizumab therapy is recommended. Anti-JCV antibody-negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status, or a false-negative test result. Retesting of anti-JCV antibody-negative patients every 6 months is recommended. Retesting low index patients who have no history of prior IS use once they reach 2 years of treatment point is recommended to inform on appropriate patient MRI monitoring

In the STRATIFY-1 clinical study, approximately 11% of patients changed serostatus from anti-JCV antibody negative to positive each year. Approximately 12-16% change serostatus from antibody negative to positive in the second-generation assay reported in Unilabs real world data over a median duration of 12 months. In the STRATIFY-2 clinical study, approximately 6% of patients changed serostatus from anti-JCV antibody positive to negative each year.

Patients who test as positive for anti-JCV antibodies at any time should be considered to be at an increased risk for developing PML, independent from any prior or subsequent antibody test results.

Testing should only be performed using an appropriate and validated assay e.g., STRATIFY JCV® DxSelect™ [Lee 2013]. The anti-JCV antibody assay should not be used to diagnose PML. The use of plasmapheresis/plasma exchange (PLEX) or intravenous immunoglobulin (IVIg) can affect meaningful interpretation of serum anti-JCV antibody testing. Patients should not be tested for anti-JCV antibodies within 2 weeks of PLEX due to removal of antibodies from the serum, or within 6 months of IVIg treatment (i.e., 6 months = 5× half-life for immunoglobulins).

2.6.2. Recommended MRI Monitoring for Early Detection of PML

In clinical practice, MRI has been shown to be a useful tool for monitoring patients with MS. It may assist in differentiating PML lesions from MS plaques in patients who develop new neurological symptoms or signs once on therapy. Frequent MRI surveillance in patients at high risk of PML may lead to an earlier diagnosis of PML and better clinical outcomes [Prosperini 2016; Scarpazza 2019; Wattjes 2015]. Recommendations for MRI monitoring are summarised below:

1. Before initiation of treatment with natalizumab, a recent (usually within 3 months) full MRI (Table 1) should be available as a reference and be repeated at least on a yearly basis. Physicians should evaluate the yearly full MRI in all patients receiving natalizumab for any signs of PML.
2. More frequent MRIs (e.g., on a 3- to 6-monthly basis) using an abbreviated protocol (Table 1) should be considered for patients at a higher risk of PML. This includes the following:
    - Patients who have all 3 risk factors for PML (i.e., are anti-JCV antibody positive **and** have received more than 2 years of natalizumab therapy **and** have received prior IS therapy)

      or

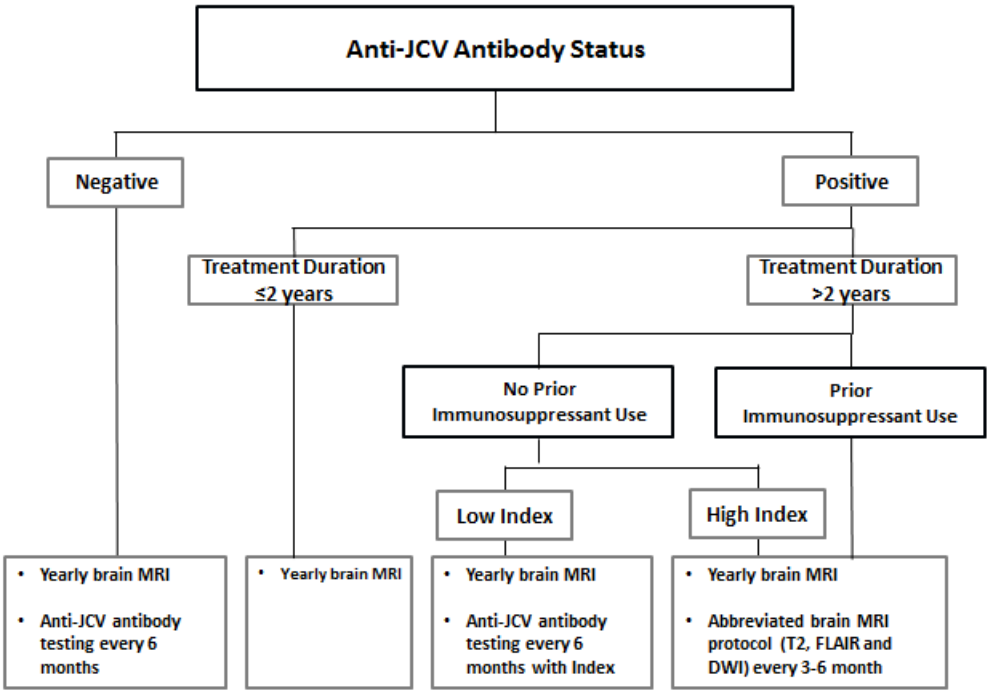
- Patients with a high anti-JCV antibody index who have received more than 2 years of natalizumab therapy and without prior history of IS therapy.

3. MRI should be performed at the first sign of any symptoms indicative of the possibility of PML.

Current evidence suggests that the risk of PML is low at an index less than or equal to 0.9 and increases substantially above 1.5 for patients who have been receiving treatment with natalizumab for more than 2 years. MRI monitoring decisions should take this information into consideration; physician discretion is advised for those patients with index values between 0.9 and 1.5.

A summary of the recommended monitoring is provided in Figure 4.

Figure 4: Recommended Patient Monitoring



DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; JCV = John Cunningham virus; MRI = magnetic resonance imaging.

Table 1: MRI Protocols

Scanner field strength > 1.5 T, slice thickness ≤ 5 mm with no gap and with whole brain coverage. Axial images prescribed from the subcallosal line.

Full MRI **Protocol**[1]	Abbreviated MRI **Protocol**[2]
• Sagittal and axial 2D FLAIR or 3D FLAIR • Axial FSE proton density/T2 • Axial DWI with ADC • Axial SE T1-weighted pre- and post-contrast or 3D T1-weighted pre- and post-contrast • Gd injection 0.1 mmol/kg over 30 seconds • 5-minute delay after contrast injection	• Sagittal and axial 2D FLAIR or sagittal 3D FLAIR with axial and coronal reformat • Axial FSE proton density/T2 • Axial DWI with ADC

[1] Baseline and routine annual scans for all patients.
[2] Safety monitoring in high-risk patients.

2D = 2 dimensional; 3D = 3 dimensional; ADC = apparent diffusion coefficient; DWI = diffusion weighted imaging; FLAIR = fluid-attenuated inversion recovery; FSE = fast spin echo; Gd = gadolinium; MRI = magnetic resonance imaging; SE = spin echo.

If MRI lesions suggestive of PML are detected, the full MRI protocol should be extended to include contrast-enhanced T1-weighted imaging to detect inflammatory features and the possible coincidence of PML and PML-immune reconstitution inflammatory syndrome (IRIS), particularly during follow-up. It is also recommended that upon request for follow-up MRI, treating physicians inform radiologists that PML or other opportunistic infections are being considered in the differential diagnosis.

2.7. Diagnosis of PML

The consensus statement on PML diagnostic criteria published by the American Academy of Neurology requires clinical, radiographic, and virologic findings or typical histopathological findings and the presence of JCV [Berger 2013]. These criteria obviate the need for a brain biopsy but require compatible clinical and MRI findings plus detection of JCV DNA in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) for a definite PML diagnosis; however, based on an alternative classification system, physicians are advised that in natalizumab-treated patients with MS, diagnosis of PML can be considered confirmed in the absence of clinical symptoms [Dong-Si 2014] (see Section 2.7.4).

In Cases of PML, these may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to;
P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000
E: postlicensing.medicinesauthority@gov.mt

Or to the local agent on behalf of the MAH:

All reports can be sent to pharmacovigilance@pharmamt.com or by post to:
103, Stuart Street,
Gzira, GZR 1054

2.7.1. Important Considerations

All natalizumab-treated patients should have regular clinical follow-up to allow for early detection of changes in neurological status. **If any new neurological symptoms in patients treated with natalizumab develop, PML should always be considered as a diagnosis.**

Patients and their partners and caregivers need to be advised of symptoms that may be indicative of early PML (see Section 3.2, Appendix 3 and Appendix 4) and receive counselling on the need to be vigilant for these symptoms while the patient is receiving natalizumab therapy and for approximately 6 months after the last dose of natalizumab (PML has been reported up to 6 months after the last dose of natalizumab in patients who did not have findings suggestive of PML at the time of discontinuation).

In all cases where further investigation of change in neurological status or change in brain MRI is indicated, natalizumab must be suspended and not restarted until non-MS pathology has been confidently excluded. Suspension of natalizumab

therapy for a short duration (days or weeks) is not expected to compromise therapeutic efficacy based on the PD of the drug (see Section 2.5). Natalizumab dosing should only be restarted when the diagnosis of PML is confidently excluded (if necessary, by repeating clinical, MRI, and laboratory investigations if suspicion of PML remains).

The decision to suspend natalizumab may be based on the initial clinical presentation, MRI findings, the evolution of symptoms or signs, and/or the response to corticosteroid treatment.

Natalizumab should be permanently discontinued if PML is confirmed.

2.7.2. Clinical Assessment

Any new or recurrent neurological symptoms should require prompt and careful evaluation in order to ascertain the underlying pathology. In a patients whose MS disease activity has been stable on natalizumab, such changes warrant a clinical suspicion of PML (or other opportunistic infection). It is important to note that the presence of new onset neurologic symptoms is not required to diagnose PML (in the setting of other confirmatory evidence) and cases of asymptomatic PML have been reported. In both high- and low-risk asymptomatic patients, any new suspected lesion on MRI should be carefully evaluated, particularly when an abbreviated protocol has been performed (see Section 2.7.3). Table 2 highlights the clinical features that may help differentiate MS lesions from PML. It should be noted that the table is not all inclusive and that symptomatic overlap between symptoms of these conditions exists. **Physicians should be aware that the clinical features of PML or other opportunistic infections can be difficult to distinguish from MS, especially early in the evolution of PML.** The history and pattern of previous and current symptoms and signs are important to note and will facilitate the management of patients.

Table 2: Clinical Features of MS and PML

	Features Indicative of:	
	MS	**PML**
Onset	Acute	Subacute
Evolution	• Over hours to days • Normally stabilise • Resolve spontaneously even without therapy	• Over weeks • Progressive
Clinical Presentation	• Diplopia • Paraesthesia • Paraparesis • Optic neuritis • Myelopathy	• Aphasia • Behavioural or cognitive changes and neuropsychological alteration • Retrochiasmal visual deficits • Marked weaknesses • Hemiparesis • Sensory deficits • Vertigo • Seizures • Ataxia (for GCN)

GCN = granule cell neuronopathy; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

Note: PML may present with other clinical features not specified in this table. PML can be detected by MRI prior to the onset of clinical features. Some overlap of clinical features of MS and PML may occur.
Reference: [Kappos 2011]

If PML is considered in a differential diagnosis, further investigations, including MRI evaluation (Table 3) and lumbar puncture and CSF evaluation, should be undertaken as soon as possible. Natalizumab dosing should be suspended until PML (or another opportunistic infection) can be ruled out.

Symptoms of JCV GCN are similar to symptoms of PML (i.e., cerebellar syndrome). In JCV GCN, serial MRI of the brain shows severe progressive cerebellar atrophy over several months and JCV DNA is detected in the CSF. Natalizumab therapy should be suspended if JCV GCN and/or PML is suspected and permanently discontinued if a diagnosis of JCV GCN and/or PML is confirmed.

2.7.3. MRI Differentiation Between PML and MS Relapse

A full MRI protocol (Table 1), preferably with and without contrast for the follow-up of patients receiving natalizumab, is proposed to obtain the best possible images to assist with clinical decision making [Yousry 2006; Yousry 2012]. Fluid-attenuated inversion recovery (FLAIR) is the most sensitive sequence for detection of PML [Wattjes 2015]. Diffusion-weighted imaging sequences may also be helpful in distinguishing new lesions from chronic MS plaques and MRI changes from a previous scan [Wattjes 2015]. The MRI sequence parameters for each scanner should be selected for good representation of CNS anatomy and visualisation of MS lesions. Consistent use of the standard MRI protocol will help with recognition of early alterations on MRI (Table 3).

The Malta Medicines Authority or the local agent on behalf of the MAH should be informed about any cases of PML.
Reports may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to;
P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000
E: postlicensing.medicinesauthority@gov.mt

Or to the local agent on behalf of the MAH:
All reports can be sent to pharmacovigilance@pharmamt.com or by post to:
103, Stuart Street,
Gzira, GZR 1054

Table 3: Features Visualised on MRI

The table shows features to be considered in the differential diagnosis of MS and PML

Feature	MS	PML
Lesion location	Focal, periventricular, or deep white matter. Lesions occur in all areas of the brain, optic nerves, and spinal cord.	Asymmetric, focal, or multifocal. Subcortical or diffuse white matter, cortical grey matter, and deep grey matter, brainstem, middle cerebellar peduncles. PML is not seen in spinal cord or optic nerves.
Lesion shape and lesion borders	Ovoid or flame shape; sharp borders, often perilesional oedema.	Irregular shape, finger-like projections toward the cortex. Ill-defined border toward the white matter, sharp border toward the grey matter.
Mode of extension	Initial enlargement over days or weeks and decrease in size within months.	Progressive increase in size.
Mass effect	Large acute lesions may have mass effect.	No mass effect.
T2-weighted images	Homogeneous hyperintensity with surrounding oedema.	Diffuse hyperintensity often with punctate microcystic inclusions. Perilesional nodules in the vicinity of the primary lesion (milky way galaxy).
T1-weighted images	Acute lesions: hypointense or isointense. Increasing signal intensity over time.	Isointense to hypointense at onset with decreasing signal intensity over time.
FLAIR images	Hyperintense, sharply delineated.	Hyperintense. Most sensitive sequence for detection of PML.
Contrast enhancement in acute lesions	Homogeneous nodular, ring or open ring enhancement conforms to shape and size of the lesion. Resolution over 1-2 months.	43% of lesions show enhancement at the time of presentation. Patchy or nodular appearance. Enhancement does not conform to size or shape of the lesion. Increased enhancement with IRIS.
DWI	Acute lesions hyperintense. Chronic lesions isointense.	Acute lesions hyperintense. Distinguishes new PML lesions within areas of chronic white matter disease. No restriction on ADC.
Atrophy	Diffuse atrophy with progressive MS disease.	Post PML-IRIS – encephalomalacia and diffuse brain atrophy in the affected areas.

ADC = apparent diffusion coefficient; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; IRIS = immune reconstitution inflammatory syndrome; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.
References: [Kappos 2011; Wattjes and Barkhof 2014; Yousry 2012]

2.7.4. Laboratory Investigation

The detection of JCV DNA by PCR in the CSF confirms the diagnosis of PML in patients with appropriate and associated MRI findings. However, a negative JCV PCR result should not exclude a possible diagnosis of PML, particularly because small volume lesions are associated with lower viral copy numbers [Wijburg 2018]. If JCV DNA is not detected in CSF and if clinical or MRI-based suspicion of PML persists despite a local or reference laboratory result being negative (i.e., not detected) for JCV DNA by PCR, a repeat lumbar puncture is recommended. Brain biopsy to detect JCV should be considered if JCV DNA is not detected in CSF on repeat testing, especially if the result is based on an assay with a limit of detection (LoD) that is higher than 11 copies/mL.

Assays should be based on quantitative real-time PCR methodology to maximise sensitivity and specificity for detection, and it is recommended to use an assay with an LoD of at least 11 copies/mL. This level of detection is diagnostically relevant because PML has been confirmed in patients with low copy numbers in the CSF.

CSF samples should be analysed as quickly as possible to facilitate the diagnosis of PML. The MAH is not in a position to certify any laboratory. However, the MAH is aware of a central laboratory (Unilabs, Copenhagen, Denmark) that offers a real-time PCR assay specific for detection of JCV DNA in the CSF.

The real-time assay at Unilabs was developed and qualified at the Translational Sciences department within the MAH and transferred to Unilabs for validation and clinical use.

Details of the procedure for the collection, handling, and transport of samples to the central facility are available from Medical Affairs in Malta.

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2.8. Management of PML

Immune reconstitution

The data available suggest that early PML recognition is important for an optimal clinical outcome [Clifford 2015; Kappos 2019].

PLEX and/or immunoadsorption (IA) has been reported for rapid removal of natalizumab from the body with the intention of accelerated restoration of CNS immunosurveillance. However, based on a retrospective analysis of natalizumab-treated patients, no difference was observed on 2-year survival after PML diagnosis between patients who received PLEX and those who did not [Kappos 2019]. Physicians should use medical judgement when considering the use of PLEX to treat PML. And, if PLEX

is used, patients should be closely monitored for the development of IRIS (see Section 2.8.1), which occurs in almost all patients treated with PLEX and appears to occur more rapidly than in patients who are not treated with PLEX [Carruthers and Berger 2014; Clifford 2010].

Antivirals and other adjuvants

To date, no clinical trial has demonstrated a beneficial effect of antiviral agents in the management of PML. Real-world reports of PML outcomes associated with use of antivirals, including mefloquine, mirtazapine, and filgrastim, are mixed and inadequate to recommend any treatment approach [Kappos 2019; Williamson and Berger 2017].

2.8.1. Treatment of Immune Reconstitution Inflammatory Syndrome

Clinical neurologic deterioration in patients with PML and/or JCV GCN may be caused by JCV mediated destruction of CNS tissue, or upon restoration of immune function, by an intracerebral immune inflammatory reaction known as immune reconstitution inflammatory syndrome (IRIS).

IRIS is generally suspected when patients with PML exhibit signs of clinical worsening usually, but not always, accompanied by gadolinium enhancement of PML lesions with or without mass effect on brain MRI. The clinical worsening is a result of a local inflammatory reaction, including oedema, and manifests as a worsening of neurological symptoms including hemiparesis, ataxia, speech abnormalities, visual disturbance, cognitive/behavioural changes, and seizures (dependent on the site of IRIS). Severe sequelae can occur including coma and death. Although JC viral load in the CSF might be expected to decline in the setting of IRIS, it is also possible that due to the breakdown of the blood brain barrier (BBB) and release of JCV from cells lysed during IRIS, it can be increased.

It may become necessary to treat the active immune reaction to prevent potential damage caused by IRIS [Elston and Thaker 2009], but it can be life threatening and may therefore require management in an intensive care unit. Therefore, following PLEX or IA, periodic clinical monitoring of patients, including MRI monitoring, may be useful for the early detection of IRIS. The diagnosis and management of IRIS is a controversial issue and there is no consensus concerning its treatment. However, it has recently been suggested that corticosteroids may be useful to treat IRIS, particularly in patients with severe to life-threatening IRIS [Clifford 2015]. The following steroid regimens have been reported for the treatment of IRIS in the literature:

1. Oral prednisone 1.5 mg/kg/day for 2 weeks with a taper over 2 months.
2. Intravenous methylprednisolone (1 g/d for 3 or 5 days) with oral taper over 2 months [Williamson and Berger 2017].

If further deterioration occurs during the steroid taper and this is judged to be due to continuing or new inflammatory reactions, a further course of higher dose steroids may be necessary.

Prophylactic steroid treatment is currently not recommended [Antoniol 2012; Scarpazza 2017].

2.9. Prognosis of PML

Improved survival from PML after natalizumab therapy has been associated with a younger age at PML diagnosis, less functional disability before PML diagnosis, a lower JCV load at PML diagnosis, and more localised brain involvement on MRI at diagnosis [Dong-Si 2015]. Furthermore, asymptomatic patients at PML diagnosis have been reported to have better survival and less functional disability than symptomatic patients at PML diagnosis [Dong-Si 2014; Prosperini 2016]. For information on outcomes associated with PLEX, see Section 2.8.

Asymptomatic PML (with a comparison to symptomatic PML)

Cases of asymptomatic PML have been reported that were initially suspected based on MRI findings and later confirmed by positive JCV DNA in the CSF.

Asymptomatic PML patients had a shorter time from suspicion of PML to diagnosis of PML compared with symptomatic PML patients (median of 11 days versus 30 days, respectively). In addition, asymptomatic PML patients had more localised PML on brain MRI at the time of suspicion compared with symptomatic PML patients. There was a higher proportion of asymptomatic PML patients who had unilobar PML lesions on MRI at the time of diagnosis compared with symptomatic PML patients (56.2% versus 36.9%, respectively). Conversely, 18.8% of asymptomatic patients had widespread PML on MRI compared with 40.8% of symptomatic patients.

Asymptomatic PML patients also had a higher survival rate compared with symptomatic patients (92.2% versus 73.1%, respectively).

2.10. PML Diagnosed After Discontinuation of Natalizumab

PML has been reported after the discontinuation of natalizumab. Patients and physicians should remain alert for any new signs or symptoms that may be suggestive of PML for approximately 6 months after discontinuation, taking into account the switch to other MS disease-modifying treatments that are associated with a risk of PML.

As of 07 August 2020, a total of 102 confirmed cases of PML have been reported in patients where PML onset occurred more than 4 weeks after the last natalizumab infusion. Of the 102 cases where time from last infusion to onset of PML is known, the majority of cases (80.0%) occurred either prior to or within 3 months of the last infusion, and 101 cases (99%) occurred within 6 months of the last infusion.

3. EDUCATIONAL GUIDANCE

Due to this increased risk of developing PML, with increasing treatment duration, the benefits and risks of natalizumab therapy should be individually reconsidered by the specialist physician and the patient. The patient should be reinformed about the risks of PML with natalizumab after 24 months and should be instructed together with their partners and caregivers on early signs and symptoms of PML. Patients who are discontinuing natalizumab therapy should also be informed that cases of PML have occurred in patients up to 6 months after the last dose of natalizumab, and the same monitoring protocol should be continued for approximately 6 months after discontinuation of natalizumab.

Patients should also be informed of the increased risk of opportunistic infections.

A template Treatment Initiation Form, Treatment Continuation Form, and Treatment Discontinuation Form are provided in Appendix 4.

3.1. Informing Patients About Benefits and Risks

The PL that is contained in each pack of natalizumab explains both benefits and risks in language designed specifically for patients to understand (this has been confirmed by MS patient readability testing). An example is included as part of this pack Appendix 2) so that the physician can become familiar with the PL prior to counselling patients about natalizumab therapy.

Physicians should counsel patients on the importance of uninterrupted dosing, particularly in the early months of treatment.

Physicians should counsel pregnant women on the use of natalizumab during pregnancy taking into account the patient's clinical condition. This benefit-risk discussion should also cover the possible return of disease activity after stopping natalizumab and the monitoring of newborns for potential haematological abnormalities for patients exposed to natalizumab in the third trimester.

In addition, locally agreed templates for a Treatment Initiation Form, a Treatment Continuation Form at 24 months of treatment, and a Treatment Discontinuation Form describing specifically the risk of PML with natalizumab therapy and the importance of monitoring for PML are provided in Appendix 4. These forms should be signed, provided to and discussed with patients before initiation of treatment, after patient counselling at 24 months of treatment, and after discontinuation to ensure that patients are fully informed about the risk of PML. The physician should keep 1 copy of these forms, and 1 copy should be given to the patient.

3.2. Patient Alert Card

The Patient Alert Card must be issued to patients to fill out and carry with them.

Partners and caregivers should also be made aware of the information provided in the Patient Alert Card. The Patient Alert Card includes a recommendation for patients to retain the card for a period of 6 months after the last dose of natalizumab therapy because signs and symptoms suggestive of opportunistic infections, including PML (e.g. changes in mood, behavior, memory, motor weakness, speech, or communication difficulties) may occur up to 6 months after discontinuation and patients and their partners and caregivers should report any suspect changes in neurological status during this time.

The card contains a space to provide contact information so that they can report these concerns. Their physician must complete this section when issuing the card.

Patient Alert Cards (see Appendix 3) are included as part of the Physician Pack. Additional cards can be ordered from the local company office; contact details are contained in the pack.

3.3. Treatment forms

Treatment forms (see Appendix 4) are included as part of the Physician Pack. Additional forms can be ordered from the local company office; contact details are contained in the pack.

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to;
P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000
E: postlicensing.medicinesauthority@gov.mt

Or to the local agent on behalf of the MAH:

All reports can be sent to pharmacovigilance@pharmamt.com or by post to:

103, Stuart Street,

Gzira, GZR 1054

The risk minimisation measures are part of the conditions of the marketing authorisation.

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APPENDIX 1. SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

Tysabri 300 mg concentrate for solution for infusion
Tysabri 150 mg solution for injection in pre-filled syring

1. NAME OF THE MEDICINAL PRODUCT

Tysabri 300 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 20 mg of natalizumab.

When diluted (see section 6.6), the solution for infusion contains approximately 2.6 mg per mL of natalizumab.

Natalizumab is a recombinant humanised anti-α4-integrin antibody produced in a murine cell line by recombinant DNA technology.

Excipient with known effect

Each vial contains 2.3 mmol (or 52 mg) sodium (see section 4.4 for further information).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Colourless, clear to slightly opalescent solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tysabri is indicated as single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) (for exceptions and information about washout periods see sections 4.4 and 5.1)

or

- Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

4.2 Posology and method of administration

Therapy is to be initiated and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions, in centres with timely access to MRI.

Patients treated with this medicinal product must be given the patient alert card and be informed about the risks of the medicinal product (see also package leaflet). After 2 years of treatment, patients should be re-informed about the risks, especially the increased risk of Progressive Multifocal Leukoencephalopathy (PML), and should be instructed together with their caregivers on early signs and symptoms of PML.

Resources for the management of hypersensitivity reactions and access to MRI should be available.

Some patients may have been exposed to immunosuppressive medicinal products (e.g. mitoxantrone, cyclophosphamide, azathioprine). These medicinal products have the potential to cause prolonged immunosuppression, even after dosing is discontinued. Therefore the physician must confirm that such patients are not immunocompromised before starting treatment (see section 4.4).

Posology

Tysabri 300 mg is administered by intravenous infusion once every 4 weeks.

Continued therapy must be carefully reconsidered in patients who show no evidence of therapeutic benefit beyond 6 months.

Data on the safety and efficacy of natalizumab at 2 years were generated from controlled, double–blind studies. After 2 years continued therapy should be considered only following a reassessment of the potential for benefit and risk. Patients should be re-informed about the risk factors for PML, like duration of treatment, immunosuppressant use prior to receiving the medicinal product and the presence of anti-John Cunningham virus (JCV) antibodies (see section 4.4).

Readministration

The efficacy of re-administration has not been established, for safety (see section 4.4).

Special populations

Elderly

This medicinal product is not recommended for use in patients aged over 65 due to a lack of data in this population.

Renal and hepatic impairment

Studies have not been conducted to examine the effects of renal or hepatic impairment.

The mechanism for elimination and results from population pharmacokinetics suggest that dose adjustment would not be necessary in patients with renal or hepatic impairment.

Paediatric population

The safety and efficacy of this medicinal product in children and adolescents up to 18 years have not been established. Currently available data are described in sections 4.8 and 5.1.

Method of administration

This medicinal product is for intravenous use.

For instructions on dilution of the medicinal product before administration (see section 6.6).

After dilution (see section 6.6), the infusion is to be administered over approximately 1 hour and patients are to be observed during the infusion and for 1 hour after the completion of the infusion for signs and symptoms of hypersensitivity reactions.

Tysabri 300 mg concentrate for solution for infusion must not be administered as a bolus injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Progressive multifocal leukoencephalopathy (PML).

Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies (see sections 4.4 and 4.8).

Combination with other DMTs.

Known active malignancies, except for patients with cutaneous basal cell carcinoma.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and batch number of the administered product should be clearly recorded.

Progressive Multifocal Leukoencephalopathy (PML)

Use of this medicinal product has been associated with an increased risk of PML, an opportunistic infection caused by JC virus, which may be fatal or result in severe disability.

Due to this increased risk of developing PML, the benefits and risks of treatment should be individually reconsidered by the specialist physician and the patient; patients must be monitored at regular intervals throughout and should be instructed together with their caregivers on early signs and symptoms of PML. JC virus also causes JCV granule cell neuronopathy (GCN) which has been reported in patients treated with this medicinal product. Symptoms of JCV GCN are similar to symptoms of PML (i.e. cerebellar syndrome).

The following risk factors are associated with an increased risk of PML:

- The presence of anti-JCV antibodies.
- Treatment duration, especially beyond 2 years. After 2 years all patients should be re-informed about the risk of PML with the medicinal product.
- Immunosuppressant use prior to receiving the medicinal product.

Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared to patients who are anti-JCV antibody negative. Patients who have all three risk factors for PML (i.e., are anti-JCV antibody positive **and** have received more than 2 years of therapy with this medicinal product **and** have received prior immunosuppressant therapy) have a significantly higher risk of PML.

In anti-JCV antibody positive natalizumab treated patients who have not used prior immunosuppressants the level of anti-JCV antibody response (index) is associated with the level of risk for PML.

In anti-JCV antibody positive patients, extended interval dosing of Tysabri (average dosing interval of approximately 6 weeks) is suggested to be associated with a lower PML risk compared to approved dosing. If utilising extended interval dosing, caution is required because the efficacy of extended interval dosing has not been established and the associated benefit risk balance is currently unknown (see section 5.1). For further information, refer to the Physician Information and Management Guidelines.

Patients considered at high risk treatment with this treatment should only be continued if the benefits outweigh the risks. For the estimation of PML risk in the different patient subgroups, please refer to the Physician Information and Management Guidelines.

<u>Anti-JCV antibody testing</u>

Anti-JCV antibody testing provides supportive information for risk stratification of treatment with this medicinal product. Testing for serum anti-JCV antibody prior to initiating therapy or in patients receiving the medicinal product with an unknown antibody status is recommended. Anti-JCV antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result. Re-testing of anti-JCV antibody negative patients every 6 months is recommended. Retesting low index patients who have no history of prior immunosuppressant use every 6 months once they reach the 2 year treatment point is recommended.

The anti-JCV antibody assay (ELISA) should not be used to diagnose PML. Use of plasmapheresis/plasma exchange (PLEX) or intravenous immunoglobulin (IVIg) can affect

meaningful interpretation of serum anti-JCV antibody testing. Patients should not be tested for anti-JCV antibodies within 2 weeks of PLEX due to removal of antibodies from the serum, or within 6 months of IVIg (i.e. 6 months = 5x half-life for immunoglobulins).

For further information on anti-JCV antibody testing please see Physician Information and Management Guidelines.

MRI screening for PML

Before initiation of treatment with this medicinal product, a recent (usually within 3 months) MRI should be available as a reference, and be repeated at least on a yearly basis. More frequent MRIs (e.g. on a 3 to 6 monthly basis) using an abbreviated protocol should be considered for patients at higher risk of PML. This includes:

- Patients who have all three risk factors for PML (i.e., are anti-JCV antibody positive **and** have received more than 2 years of therapy with this medicinal product **and** have received prior immunosuppressant therapy),

or

- Patients with a high anti-JCV antibody index who have received more than 2 years of therapy with this medicinal product and without prior history of immunosuppressant therapy.

Current evidence suggests that the risk of PML is low at an index equal to or below 0.9 and increases substantially above 1.5 for patients who have been on treatment with this medicinal product for longer than 2 years (see the Physician Information and Management Guidelines for further information).

No studies have been performed to evaluate the efficacy and safety of natalizumab when switching patients from DMTs with an immunosuppressant effect. It is unknown if patients switching from these therapies to this treatment have an increased risk of PML, therefore these patients should be monitored more frequently (i.e. similarly to patients switching from immunosuppressants to natalizumab).

PML should be considered as a differential diagnosis in any MS patient taking Tysabri presenting with neurological symptoms and/or new brain lesions in MRI. Cases of asymptomatic PML based on MRI and positive JCV DNA in the cerebrospinal fluid have been reported.

Physicians should refer to the Physician Information and Management Guidelines for further information on managing the risk of PML in natalizumab-treated patients.

If PML or JCV GCN is suspected, further dosing must be suspended until PML has been excluded.

The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction and, if so, whether these symptoms are typical of MS or possibly suggestive of PML or JCV GCN. If any doubt exists, further evaluation, including MRI scan preferably with contrast (compared with pre-treatment baseline MRI), CSF testing for JC Viral DNA and repeat neurological assessments, should be considered as described in the Physician Information and Management Guidelines (see Educational guidance). Once the

clinician has excluded PML and/or JCV GCN (if necessary, by repeating clinical, imaging and/or laboratory investigations if clinical suspicion remains), dosing may resume.

The physician should be particularly alert to symptoms suggestive of PML or JCV GCN that the patient may not notice (e.g. cognitive, psychiatric symptoms or cerebellar syndrome). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

PML has been reported following discontinuation of this medicinal product in patients who did not have findings suggestive of PML at the time of discontinuation. Patients and physicians should continue to follow the same monitoring protocol and be alert for any new signs or symptoms that may be suggestive of PML for approximately 6 months following discontinuation of TYSABRI.

If a patient develops PML the dosing of natalizumab must be permanently discontinued.

Following reconstitution of the immune system in immunocompromised patients with PML improved outcome has been seen.

Based on a retrospective analysis of natalizumab-treated patients since its approval, no difference was observed on 2-year survival after PML diagnosis between patients who received PLEX and those who did not. For other considerations on the management of PML, see the Physician Information and Management Guidelines.

PML and IRIS (Immune Reconstitution Inflammatory Syndrome)

IRIS occurs in almost all PML patients treated with this medicinal product after withdrawal or removal of the medicinal product. IRIS is thought to result from the restoration of immune function in patients with PML, which can lead to serious neurological complications and may be fatal. Monitoring for development of IRIS and appropriate treatment of the associated inflammation during recovery from PML should be undertaken (see the Physician Information and Management Guidelines for further information).

Infections including other opportunistic infections

Other opportunistic infections have been reported with use of this medicinal product, primarily in patients with Crohn’s disease who were immunocompromised or where significant co-morbidity existed, however increased risk of other opportunistic infections with use of the medicinal product in patients without these co-morbidities cannot currently be excluded. Opportunistic infections were also detected in MS patients treated with this medicinal product as a monotherapy (see section 4.8).

This treatment increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses. Serious, life-threatening, and sometimes fatal cases have been reported in the postmarketing setting in multiple sclerosis patients receiving the treatment (see section 4.8). If herpes encephalitis or meningitis occurs, the medicinal product should be discontinued, and appropriate treatment for herpes encephalitis or meningitis should be administered.

Acute retinal necrosis (ARN) is a rare fulminant viral infection of the retina caused by the family of herpes viruses (e.g. varicella zoster). ARN has been observed in patients being administered this medicinal product and can be potentially blinding. Patients presenting with eye symptoms such as decreased visual acuity, redness and painful eye should be referred for retinal screening for ARN. Following clinical diagnosis of ARN, discontinuation of this medicinal product should be considered in these patients.

Prescribers should be aware of the possibility that other opportunistic infections may occur during therapy and should include them in the differential diagnosis of infections that occur in natalizumab-treated patients. If an opportunistic infection is suspected, dosing is to be suspended until such infections can be excluded through further evaluations.

If a patient receiving this medicinal product develops an opportunistic infection, dosing of the medicinal product must be permanently discontinued.

Educational guidance

All physicians who intend to prescribe the medicinal product must ensure they are familiar with the Physician Information and Management Guidelines.

Physicians must discuss the benefits and risks of natalizumab therapy with the patient and provide them with a patient alert card. Patients should be instructed that if they develop any infection then they should inform their physician that they are being treated with this medicinal product.

Physicians should counsel patients on the importance of uninterrupted dosing, particularly in the early months of treatment (see hypersensitivity).

Hypersensitivity

Hypersensitivity reactions have been associated with this medicinal product, including serious systemic reactions (see section 4.8). These reactions usually occurred during the infusion or up to 1 hour after completion of the infusion. The risk for hypersensitivity was greatest with early infusions and in patients re-exposed to treatment following an initial short exposure (one or two infusions) and extended period (three months or more) without treatment. However, the risk of hypersensitivity reactions should be considered for every infusion administered.

Patients are to be observed during the infusion and for 1 hour after the completion of the infusion (see section 4.8). Resources for the management of hypersensitivity reactions should be available.

This product should be discontinued and appropriate therapy initiated at the first symptoms or signs of hypersensitivity.

Patients who have experienced a hypersensitivity reaction must be permanently discontinued from treatment with natalizumab.

Concurrent treatment with immunosuppressants

The safety and efficacy of this medicinal product in combination with other immunosuppressive and antineoplastic therapies have not been fully established. Concurrent use of these agents with this medicinal product may increase the risk of infections, including opportunistic infections, and is contraindicated (see section 4.3).

In phase 3 MS clinical trials, concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection. Short courses of corticosteroids can be used in combination with this medicinal product.

Prior treatment with immunosuppressive or immunomodulatory therapies

Patients with a treatment history of immunosuppressant medications are at increased risk for PML.
No studies have been performed to evaluate the efficacy and safety of the medicinal product when switching patients from DMTs with an immunosuppressant effect. It is unknown if patients switching from these therapies to this medicinal product have an increased risk of PML, therefore these patients should be monitored more frequently (i.e. similarly to patients switching from immunosuppressants to this medicinal product, see MRI screening for PML).

Care should be taken with patients who have previously received immunosuppressants to allow sufficient time for immune function recovery to occur. Physicians must evaluate each individual case to determine whether there is evidence of an immunocompromised state prior to commencing treatment (see section 4.3).

When switching patients from another DMT to this medicinal product, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation. A Complete Blood Count (CBC, including lymphocytes) is recommended prior to initiating treatment to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved.

Patients can switch directly from beta interferon or glatiramer acetate to natalizumab providing there are no signs of relevant treatment-related abnormalities e.g. neutropenia and, lymphopenia.

When switching from dimethyl fumarate, the washout period should be sufficient for lymphocyte count to recover before treatment is started.

Following discontinuation of fingolimod, lymphocyte count progressively returns to normal range within 1 to 2 months after stopping therapy. The washout period should be sufficient for lymphocyte count to recover before treatment is started.

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, clearance of teriflunomide from plasma can take from several months up to 2 years. An accelerated elimination procedure as defined in the teriflunomide Summary of Product Characteristics is recommended or alternatively washout period should not be shorter than 3.5 months. Caution regarding potential concomitant immune effects is required when switching patients from teriflunomide to this medicinal product.

Alemtuzumab has profound prolonged immunosuppressive effects. As the actual duration of these effects is unknown, initiating treatment with this medicinal product after alemtuzumab is not recommended unless the benefits clearly outweigh the risks for the individual patient.

Immunogenicity

Disease exacerbations or infusion related events may indicate the development of antibodies against natalizumab. In these cases the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after at least 6 weeks, treatment should be discontinued, as persistent antibodies are associated with a substantial decrease in efficacy of this medicinal product and an increased incidence of hypersensitivity reactions (see section 4.8).

Since patients who have received an initial short exposure to this medicinal product and then had an extended period without treatment are at a higher risk of developing anti-natalizumab antibodies and/or hypersensitivity upon redosing, the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after at least 6 weeks, the patient should not receive further treatment with natalizumab (see section 5.1).

Hepatic events

Spontaneous serious adverse reactions of liver injury have been reported during the post-marketing phase (see section 4.8). These liver injuries may occur at any time during treatment, even after the first dose. In some instances, the reaction reoccurred when treatment was reintroduced. Some patients with a past medical history of an abnormal liver test have experienced an exacerbation of abnormal liver test while on treatment. Patients should be monitored as appropriate for impaired liver function, and be instructed to contact their physician in case signs and symptoms suggestive of liver injury occur, such as jaundice and vomiting. In cases of significant liver injury this medicinal product should be discontinued.

Stopping therapy

If a decision is made to stop treatment with natalizumab, the physician needs to be aware that natalizumab remains in the blood, and has pharmacodynamic effects (e.g increased lymphocyte counts) for approximately 12 weeks following the last dose. Starting other therapies during this interval will result in a concomitant exposure to natalizumab. For medicinal products such as interferon and glatiramer acetate, concomitant exposure of this duration was not associated with safety risks in clinical trials. No data are available in MS patients regarding concomitant exposure with immunosuppressant medication. Use of these medicinal products soon after the discontinuation of natalizumab may lead to an additive immunosuppressive effect. This should be carefully considered on a case-by-case basis, and a wash-out period of natalizumab might be appropriate. Short courses of steroids used to treat relapses were not associated with increased infections in clinical trials.

Sodium content

Before dilution, this medicinal product contains 52 mg sodium per vial of medicinal product, equivalent to 2.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Natalizumab is contraindicated in combination with other DMTs (see section 4.3).

Immunisations

In a randomised, open label study of 60 patients with relapsing MS there was no significant difference in the humoral immune response to a recall antigen (tetanus toxoid) and only slightly slower and reduced humoral immune response to a neoantigen (keyhole limpet haemocyanin) was observed in patients who were treated with this medicinal product for 6 months compared to an untreated control group. Live vaccines have not been studied.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

If a woman becomes pregnant while taking this medicinal product, discontinuation should be considered. A benefit-risk evaluation of the use of this medicinal product during pregnancy should take into account the patient's clinical condition and the possible return of disease activity after stopping the medicinal product.

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3).

Data from clinical trials, a prospective pregnancy registry, post-marketing cases and available literature do not suggest an effect of natalizumab exposure on pregnancy outcomes.

The completed prospective Tysabri pregnancy registry contained 355 pregnancies with available outcomes. There were 316 live births, 29 of which were reported to have birth defects. Sixteen of the 29 were classified as major defects. The rate of defects corresponds to the defect rates reported in other pregnancy registries involving MS patients. There is no evidence of a specific pattern of birth defects with this medicinal product.

Cases from published literature reported transient mild to moderate thrombocytopenia and anaemia observed in infants born to women exposed to natalizumab in their third trimester of pregnancy. Therefore, it is recommended that newborns of women exposed to the medicinal product during the third trimester of pregnancy are monitored for potential haematological abnormalities.

Breast-feeding

Natalizumab is excreted in human milk. The effect of natalizumab on newborn/infants is unknown. Breast-feeding should be discontinued during treatment with natalizumab.

Fertility

Reductions in female guinea pig fertility were observed in one study at doses in excess of the human dose; natalizumab did not affect male fertility. It is considered unlikely that

natalizumab will affect fertility performance in humans following the maximum recommended dose.

4.7 Effects on ability to drive and use machines

Tysabri has a minor influence on the ability to drive and use machines. Dizziness may occur following administration of this medicinal product (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In placebo-controlled trials in 1,617 MS patients treated with natalizumab for up to 2 years (placebo: 1,135), adverse events leading to discontinuation of therapy occurred in 5.8% of patients treated with natalizumab (placebo: 4.8%). Over the 2-year duration of the studies, 43.5% of patients treated with natalizumab reported adverse reactions (placebo: 39.6%).

In clinical trials in 6786 patients treated with natalizumab (intravenous infusion and subcutaneous injection), the most frequently occurring adverse reactions were headache (32%), nasopharyngitis (27%), fatigue (23%), urinary tract infection (16%), nausea (15%), arthralgia (14%), and dizziness (11%) associated with natalizumab administration.

Tabulated list of adverse reactions

Adverse reactions arising from clinical studies, post-authorisation safety studies and spontaneous reports are presented in Table 1, below. Within the system organ classes they are listed under the following headings: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions

MedDRA System Organ Class	Frequency of adverse reactions				
	Very Common	*Common*	*Uncommon*	*Rare*	*Not known*
Infections and infestations	Nasopharyngitis Urinary tract infection	Herpes infection	Progressive multifocal leukoencephalopathy	Herpes ophthalmic	Meningoencephalitis herpetic JC virus granule cell neuropathy Necrotising herpetic retinopathy
Immune system disorders		Hypersensitivity	Anaphylactic reaction Immune reconstitution inflammatory syndrome		
Blood and lymphatic system disorders		Anaemia	Eosinophilia	Haemolytic anaemia Nucleated red cells	

MedDRA System Organ Class	Frequency of adverse reactions				
	Very Common	*Common*	*Uncommon*	*Rare*	*Not known*
Hepatobiliary disorders				Hyperbilirubinaemia	Liver injury
Investigations		Hepatic enzyme increased Drug specific antibody present			
Injury, poisoning and procedural complications	Infusion related reaction				
Respiratory, thoracic and mediastinal disorders		Dyspnoea			
Gastrointestinal disorders	Nausea	Vomiting			
General disorders and administration site conditions	Fatigue	Pyrexia Chills Infusion site reaction Injection site reaction	Face oedema		
Skin and subcutaneous tissue disorders		Pruritus Rash Urticaria		Angioedema	
Vascular disorders		Flushing			
Nervous system disorders	Dizziness Headache				
Musculoskeletal and connective tissue disorders	Arthralgia				

Description of selected adverse reactions

Infusion-related reactions (IRR)

In 2-year controlled clinical trials in MS patients, an infusion-related event was defined as an adverse event occurring during the infusion or within 1 hour of the completion of the infusion. These occurred in 23.1% of MS patients treated with natalizumab (placebo: 18.7%). Events reported more commonly with natalizumab than with placebo included dizziness, nausea, urticaria and rigors.

Hypersensitivity reactions

In 2-year controlled clinical trials in MS patients, hypersensitivity reactions occurred in up to 4% of patients. Anaphylactic/anaphylactoid reactions occurred in less than 1% of patients receiving this medicinal product. Hypersensitivity reactions usually occurred during the infusion or within the 1-hour period after the completion of the infusion (see section 4.4). In

post-marketing experience, there have been reports of hypersensitivity reactions which have occurred with one or more of the following associated symptoms: hypotension, hypertension, chest pain, chest discomfort, dyspnoea, angioedema, in addition to more usual symptoms such as rash and urticaria.

Immunogenicity

In 10% of patients antibodies against natalizumab were detected in 2-year controlled clinical trials in MS patients. Persistent anti-natalizumab antibodies (one positive test reproducible on retesting at least 6 weeks later) developed in approximately 6% of patients. Antibodies were detected on only one occasion in an additional 4% of patients. Persistent antibodies were associated with a substantial decrease in the effectiveness of natalizumab and an increased incidence of hypersensitivity reactions. Additional infusion-related reactions associated with persistent antibodies included rigors, nausea, vomiting and flushing (see section 4.4).

If, after approximately 6 months of therapy, persistent antibodies are suspected, either due to reduced efficacy or due to occurrence of infusion-related events, they may be detected and confirmed with a subsequent test 6 weeks after the first positive test. Given that efficacy may be reduced or the incidence of hypersensitivity or infusion-related reactions may be increased in a patient with persistent antibodies, treatment should be discontinued in patients who develop persistent antibodies.

Infections, including PML and opportunistic infections

In 2-year controlled clinical trials in MS patients, the rate of infection was approximately 1.5 per patient-year in both natalizumab- and placebo-treated patients. The nature of the infections was generally similar in natalizumab- and placebo-treated patients. A case of *cryptosporidium* diarrhoea was reported in MS clinical trials. In other clinical trials, cases of additional opportunistic infections have been reported, some of which were fatal. The majority of patients did not interrupt natalizumab therapy during infections and recovery occurred with appropriate treatment.

In clinical trials, herpes infections (Varicella-Zoster virus, Herpes-simplex virus) occurred slightly more frequently in natalizumab-treated patients than in placebo-treated patients. In post-marketing experience, serious, life-threatening, and sometimes fatal cases of encephalitis and meningitis caused by herpes simplex or varicella zoster have been reported in multiple sclerosis patients receiving natalizumab. The duration of treatment with natalizumab prior to onset ranged from a few months to several years (see section 4.4).

In postmarketing experience, rare cases of ARN have been observed in patients receiving this medicinal product. Some cases have occurred in patients with central nervous system (CNS) herpes infections (e.g. herpes meningitis and encephalitis). Serious cases of ARN, either affecting one or both eyes, led to blindness in some patients. The treatment reported in these cases included anti-viral therapy and in some cases, surgery (see section 4.4).

Cases of PML have been reported from clinical trials, post-marketing observational studies and post-marketing passive surveillance. PML usually leads to severe disability or death (see section 4.4). Cases of JCV GCN have also been reported during postmarketing use of Tysabri. Symptoms of JCV GCN are similar to PML.

Hepatic events

Spontaneous cases of serious liver injuries, increased liver enzymes, hyperbilirubinaemia have been reported during the post-marketing phase (see section 4.4).

Anaemia and haemolytic anaemia

Rare, serious cases of anaemia and haemolytic anaemia have been reported in patients treated with this medicinal product in post-marketing observational studies.

Malignancies

No differences in incidence rates or the nature of malignancies between natalizumab- and placebo-treated patients were observed over 2 years of treatment. However, observation over longer treatment periods is required before any effect of natalizumab on malignancies can be excluded (see section 4.3).

Effects on laboratory tests

In 2-year controlled clinical trials in MS patients treatment with natalizumab was associated with increases in circulating lymphocytes, monocytes, eosinophils, basophils and nucleated red blood cells. Elevations in neutrophils were not seen. Increases from baseline for lymphocytes, monocytes, eosinophils and basophils ranged from 35% to 140% for individual cell types but mean cell counts remained within normal ranges with IV administration. During treatment with IV form of this medicinal product, small reductions in haemoglobin (mean decrease 0.6 g/dL), haematocrit (mean decrease 2%) and red blood cell counts (mean decrease 0.1 x 10^6/L) were seen. All changes in haematological variables returned to pre-treatment values, usually within 16 weeks of last dose of the medicinal product and the changes were not associated with clinical symptoms. In post-marketing experience, there have also been reports of eosinophilia (eosinophil count >1,500/mm^3) without clinical symptoms. In such cases where therapy was discontinued the elevated eosinophil levels resolved.

Paediatric population

Serious adverse events were evaluated in 621 MS paediatric patients included in a meta-analysis (see also section 5.1). Within the limitations of these data, there were no new safety signals identified in this patient population. 1 case of herpes meningitis was reported in the meta-analysis. No cases of PML were identified in the meta-analysis, however, PML has been reported in natalizumab-treated paediatric patients in the post-marketing setting.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

Malta
ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

United Kingdom (Northern Ireland)
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Safety of doses higher than 300 mg has not been adequately evaluated. The maximum amount of natalizumab that can be safely administered has not been determined.

There is no known antidote for natalizumab overdose. Treatment consists of discontinuation of the medicinal product and supportive therapy as needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA23

Pharmacodynamic effects

Natalizumab is a selective adhesion-molecule inhibitor and binds to the α4-subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the α4β1 integrin, blocking the interaction with its cognate receptor, vascular cell adhesion molecule-1 (VCAM-1), and ligands osteopontin, and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). Natalizumab blocks the interaction of α4β7 integrin with the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site, and inhibit further recruitment of immune cells into inflamed tissues.

In MS, lesions are believed to occur when activated T-lymphocytes cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and endothelial cells of the vessel wall. The interaction between α4β1 and its targets is an important component of pathological inflammation in the brain and disruption of these interactions leads to reduced inflammation. Under normal conditions, VCAM-1 is not expressed in the brain parenchyma. However, in the presence of pro-inflammatory cytokines, VCAM-1 is upregulated on endothelial cells and possibly on glial cells near the sites of inflammation. In the setting of central nervous system (CNS) inflammation in MS, it is the interaction of α4β1 with VCAM-1, CS-1 and osteopontin that

mediates the firm adhesion and transmigration of leukocytes into the brain parenchyma and may perpetuate the inflammatory cascade in CNS tissue. Blockade of the molecular interactions of α4β1 with its targets reduces inflammatory activity present in the brain in MS and inhibits further recruitment of immune cells into inflamed tissue, thus reducing the formation or enlargement of MS lesions.

Clinical efficacy

AFFIRM clinical study

Efficacy as monotherapy has been evaluated in one randomised, double-blind, placebo-controlled study lasting 2 years (AFFIRM study) in RRMS patients who had experienced at least 1 clinical relapse during the year prior to entry and had a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5. Median age was 37 years, with a median disease duration of 5 years. The patients were randomised with a 2:1 ratio to receive Tysabri 300 mg (n = 627) or placebo (n = 315) every 4 weeks for up to 30 infusions. Neurological evaluations were performed every 12 weeks and at times of suspected relapse. MRI evaluations for T1-weighted gadolinium (Gd)-enhancing lesions and T2-hyperintense lesions were performed annually.

Study features and results are presented in the Table 2.

Table 2. AFFIRM study: Main features and results

Design	Monotherapy; randomised double-blind placebo-controlled parallel-group trial for 120 weeks	
Subjects	RRMS (McDonald criteria)	
Treatment	Placebo / Natalizumab 300 mg i.v. every 4 weeks	
One year endpoint	Relapse rate	
Two year endpoint	Progression on EDSS	
Secondary endpoints	Relapse rate derived variables / MRI-derived variables	
Subjects	Placebo	Natalizumab
Randomised	315	627
Completing 1 years	296	609
Completing 2 years	285	589
Age yrs, median (range)	37 (19-50)	36 (18-50)
MS-history yrs, median (range)	6.0 (0-33)	5.0 (0-34)
Time since diagnosis, yrs median (range)	2.0 (0-23)	2.0 (0-24)
Relapses in previous 12 months, median (range)	1.0 (0-5)	1.0 (0-12)
EDSS-baseline, median (range)	2 (0-6.0)	2 (0-6.0)
RESULTS		
Annual relapse rate		
After one year (primary endpoint)	0.805	0.261
After two years	0.733	0.235
One year	Rate ratio 0.33 $CI_{95\%}$ 0.26 ; 0.41	

Table 2. AFFIRM study: Main features and results		
Two years	Rate ratio 0.32 $CI_{95\%}$ 0.26 ; 0.40	
Relapse free		
After one year	53%	76%
After two years	41%	67%
Disability		
Proportion progressed[1](12-week confirmation; primary outcome)	29%	17%
	Hazard ratio 0.58, $CI_{95\%}$ 0.43; 0.73, p<0.001	
Proportion progressed[1](24-week confirmation)	23%	11%
	Hazard ratio 0.46, $CI_{95\%}$ 0.33; 0.64, p<0.001	
MRI (0-2 years)		
Median % change in T2-hyperintense lesion volume	+8.8%	-9.4% (p<0.001)
Mean number of new or newly-enlarging T2-hyperintense lesions	11.0	1.9 (p<0.001)
Mean number of T1-hypointense lesions	4.6	1.1 (p<0.001)
Mean number of Gd-enhancing lesions	1.2	0.1 (p<0.001)

[1] Progression of disability was defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 12 or 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS =0 sustained for 12 or 24 weeks.

In the sub-group of patients indicated for treatment of rapidly evolving RRMS (patients with 2 or more relapses and 1 or more Gd+ lesion), the annualised relapse rate was 0.282 in the natalizumab-treated group (n = 148) and 1.455 in the placebo group (n = 61) (p <0.001). Hazard ratio for disability progression was 0.36 (95% CI: 0.17, 0.76) p = 0.008. These results were obtained from a *post hoc* analysis and should be interpreted cautiously. No information on the severity of the relapses before inclusion of patients in the study is available.

Tysabri Observational Program (TOP)

Interim analysis of results (as of May 2015) from the ongoing Tysabri Observational Program (TOP), a phase 4, multicentre, single-arm study (n =5,770) demonstrated that patients switching from beta interferon (n = 3,255) or glatiramer acetate (n = 1,384) to Tysabri showed a sustained, significant decrease in annualised relapse rate (p < 0.0001). Mean EDSS scores remained stable over 5 years. Consistent with efficacy results observed for patients switching from beta interferon or glatiramer acetate to Tysabri, for patients switching from fingolimod (n = 147) to this medicinal product, a significant decrease in annualised relapse rate (ARR) was observed, which remained stable over 2 years, and mean EDSS scores remained similar from baseline to Year 2. The limited sample size and shorter duration of natalizumab exposure for this subgroup of patients should be considered when interpreting these data.

Paediatric population

A post-marketing meta-analysis was conducted using data from 621 paediatric MS patients treated with natalizumab (median age 17 years, range was 7 to 18 years, 91% aged ≥14 years). Within this analysis, a limited subset of patients with data available prior to treatment (158 of the 621 patients) demonstrated a reduction in ARR from 1.466 (95% CI 1.337, 1.604) prior to treatment to 0.110 (95% CI 0.094, 0.128).

Extended interval dosing

In a pre-specified, retrospective analysis of US anti-JCV antibody positive Tysabri patients intravenously administered (TOUCH registry), the risk of PML was compared between patients treated with the approved dosing interval and patients treated with extended interval dosing as identified in the last 18 months of exposure (EID, average dosing intervals of approximately 6 weeks). The majority (85%) of patients dosed with EID had received the approved dosing for ≥1 year prior to switching to EID. The interim analysis showed a lower risk of PML in patients treated with EID (hazard ratio = 0.06, 95% CI of hazard ratio = 0.01 to 0.22). The efficacy of this medicinal product when administered with EID has not been established, and therefore the benefit/risk balance of EID is unknown (see section 4.4).

Efficacy has been modelled for patients who switch to longer dosing after ≥1 year of approved dosing with this medicinal product under intravenous administration and who did not experience a relapse in the year prior to switching. Current pharmacokinetic/pharmacodynamic statistical modelling and simulation indicate that the risk of MS disease activity for patients switching to longer dosing intervals may be higher for patients with body weight >80kg or those with dosing intervals ≥7 weeks. No prospective clinical studies have been completed to validate these findings.

5.2 Pharmacokinetic properties

Following the repeat intravenous administration of a 300 mg dose of natalizumab to MS patients, the mean maximum observed serum concentration was 110 ± 52 μg/mL. Mean average steady-state trough natalizumab concentrations over the dosing period ranged from 23 μg/mL to 29 μg/mL. The predicted time to steady state was approximately 24 weeks. An updated population pharmacokinetic analysis was conducted consisting of 11 studies and data with serial PK sampling as measured by an industry standard assay. It included over 1,286 subjects receiving doses ranging from 1 to 6 mg/kg and fixed doses of 150/300 mg.

Distribution

Median steady-state volume of distribution was 5.58 L (5.27-5.92 L, 95% confidence interval).

Elimination

Population median estimate for linear clearance was 6.21 mL/h (5.60-6.70 mL/h, 95% confidence interval) and the estimated median half-life was 26.8 days. The 95th percentile interval of the terminal half-life is from 11.6 to 46.2 days.

The population analysis of 1,286 patients explored the effects of selected covariates including body weight, age, gender, presence of anti-natalizumab antibodies and formulation on pharmacokinetics. Only body weight, the presence of anti-natalizumab antibodies and the formulation used in phase 2 studies were found to influence natalizumab disposition. Natalizumab clearance increased with body weight in a less-than-proportional manner, such that a +/-43% change in body weight resulted in only a -38% to 36% change in clearance. The presence of persistent anti-natalizumab antibodies increased natalizumab clearance approximately 2.54-fold, consistent with reduced serum natalizumab concentrations observed in persistently antibody-positive patients.

Special Populations

Paediatric population

The pharmacokinetics of natalizumab in paediatric MS patients has not been established.

Renal impairment

The pharmacokinetics of natalizumab in patients with renal insufficiency has not been studied.

Hepatic impairment

The pharmacokinetics of natalizumab in patients with hepatic insufficiency has not been studied.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Consistent with the pharmacological activity of natalizumab, altered trafficking of lymphocytes was seen as white blood cell increases as well as increased spleen weights in most *in vivo* studies. These changes were reversible and did not appear to have any adverse toxicological consequences.

In studies conducted in mice, growth and metastasis of melanoma and lymphoblastic leukaemia tumour cells was not increased by the administration of natalizumab.

No clastogenic or mutagenic effects of natalizumab were observed in the Ames or human chromosomal aberration assays. Natalizumab showed no effects on *in vitro* assays of α4-integrin-positive tumour line proliferation or cytotoxicity.

Reductions in female guinea pig fertility were observed in one study at doses in excess of the human dose; natalizumab did not affect male fertility.

The effect of natalizumab on reproduction was evaluated in 5 studies, 3 in guinea pigs and 2 in *cynomolgus* monkeys. These studies showed no evidence of teratogenic effects or effects on growth of offspring. In one study in guinea pigs, a small reduction in pup survival was noted. In a study in monkeys, the number of abortions was doubled in the natalizumab

30 mg/kg treatment groups versus matching control groups. This was the result of a high incidence of abortions in treated groups in the first cohort that was not observed in the second cohort. No effects on abortion rates were noted in any other study. A study in pregnant *cynomolgus* monkeys demonstrated natalizumab-related changes in the foetus that included mild anaemia, reduced platelet counts, increased spleen weights and reduced liver and thymus weights. These changes were associated with increased splenic extramedullary haematopoiesis, thymic atrophy and decreased hepatic haematopoiesis. Platelet counts were also reduced in offspring born to mothers treated with natalizumab until parturition, however there was no evidence of anaemia in these offspring. All changes were observed at doses in excess of the human dose and were reversed upon clearance of natalizumab.

In *cynomolgus* monkeys treated with natalizumab until parturition, low levels of natalizumab were detected in the breast milk of some animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate, monobasic, monohydrate
Sodium phosphate, dibasic, heptahydrate
Sodium chloride
Polysorbate 80 (E 433)
Water for injections

6.2 Incompatibilities

Tysabri 300 mg concentrate for solution for infusion must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

4 years

Diluted solution

After dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, immediate use is recommended. If not used immediately, the diluted solution must be stored at 2˚C to 8˚C and infused within 8 hours of dilution. In-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2˚C to 8˚C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product see section 6.3.

6.5 Nature and contents of container

15 mL concentrate in a vial (type I glass) with a stopper (chlorobutyl rubber) and a seal (aluminium) with a flip-off cap.

Pack size of one vial per carton.

6.6 Special precautions for disposal and other handling

Instructions for use:

- Inspect the vial for particles prior to dilution and administration. If particles are observed and/or the liquid in the vial is not colourless, clear to slightly opalescent, the vial must not be used.
- Use aseptic technique when preparing the solution for intravenous (IV) infusion. Remove flip-off cap from the vial. Insert the syringe needle into the vial through the centre of the rubber stopper and remove 15 mL concentrate for solution for infusion.
- Add the 15 mL concentrate for solution for infusion to 100 mL sodium chloride 9 mg/mL (0.9%) solution for injection. Gently invert the solution to mix completely. Do not shake.
- This medicinal product must not be mixed with other medicinal products or diluents.
- Visually inspect the diluted medicinal product for particles or discolouration prior to administration. Do not use if it is discoloured or if foreign particles are seen.
- The diluted medicinal product is to be used as soon as possible and within 8 hours of dilution. If the diluted medicinal product is stored at 2˚C to 8˚C (do not freeze), allow the solution to warm to room temperature prior to infusion.
- The diluted solution is to be infused intravenously over 1 hour at a rate of approximately 2 mL per minute.
- After the infusion is complete, flush the intravenous line with sodium chloride 9 mg/mL (0.9%) solution for injection.
- Each vial is for single–use only.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/346/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th June 2006
Date of latest renewal: 18th April 2016

10. DATE OF REVISION OF THE TEXT

03/2021

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Tysabri 150 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 150 mg of natalizumab.

Natalizumab is a recombinant humanised anti-α4-integrin antibody produced in a murine cell line by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Colourless to slightly yellow, slightly opalescent to opalescent solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tysabri is indicated as single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) (for exceptions and information about washout periods see sections 4.4 and 5.1)

or

- Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

4.2 Posology and method of administration

Therapy is to be initiated and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions, with timely access to MRI. Home treatment is not recommended. Administration is to be performed by a healthcare professional and patients must be monitored for early signs and symptoms of Progressive Multifocal Leukoencephalopathy (PML).
Patients treated with this medicinal product must be given the patient alert card and be informed about the risks of the medicinal product (see also package leaflet). After 2 years of treatment, patients should be re-informed about the risks especially the increased risk of

PML, and should be instructed together with their caregivers on early signs and symptoms of PML.

Resources for the management of hypersensitivity reactions and access to MRI should be available. There are limited data for the subcutaneous formulation in the Tysabri naïve patient population (see section 4.4).

Some patients may have been exposed to immunosuppressive medicinal products (e.g. mitoxantrone, cyclophosphamide, azathioprine). These medicinal products have the potential to cause prolonged immunosuppression, even after dosing is discontinued. Therefore the physician must confirm that such patients are not immunocompromised before starting treatment (see section 4.4).

Posology

The recommended dose for subcutaneous administration is 300 mg every 4 weeks. As each pre-filled syringe contains 150 mg natalizumab two pre-filled syringes need to be administered to the patient.

Continued therapy must be carefully reconsidered in patients who show no evidence of therapeutic benefit beyond 6 months.

Data on the safety and efficacy of natalizumab (intravenous infusion) at 2 years were generated from controlled, double–blind studies. After 2 years continued therapy should be considered only following a reassessment of the potential for benefit and risk. Patients should be re-informed about the risk factors for PML, like duration of treatment, immunosuppressant use prior to receiving the medicinal product and the presence of anti-John Cunningham virus (JCV) antibodies (see section 4.4).

Readministration

The efficacy of re-administration has not been established (for safety, see section 4.4).

Any switch in route of administration of the medicinal product should be made 4 weeks after the previous dose.

Special populations

Elderly

This medicinal product is not recommended for use in patients aged over 65 due to a lack of data in this population.

Renal and hepatic impairment

Studies have not been conducted to examine the effects of renal or hepatic impairment.

The mechanism for elimination and results from population pharmacokinetics suggest that dose adjustment would not be necessary in patients with renal or hepatic impairment.

Paediatric population

The safety and efficacy of this medicinal product in children and adolescents up to 18 years have not been established. Currently available data are described in sections 4.8 and 5.1.

Method of administration

For subcutaneous injection by a healthcare professional.

Injections of two pre-filled syringes should be administered (total dose 300 mg), one after the other without significant delay. The second injection should be administered no later than 30 minutes after the first injection.

The sites for subcutaneous injection are the thigh, abdomen, or the posterior aspect of the upper arm. The injection should not be made into an area of the body where the skin is irritated, reddened, bruised, infected, or scarred in any way. When removing the syringe from the injection site, the plunger should be let go of while pulling the needle straight out. Letting go of the plunger will allow the needle guard to cover the needle. The second injection should be more than 3 cm away from the first injection location (see instructions for administration at the end of the package leaflet).

Patients are to be observed during the subcutaneous injections and for 1 hour after for signs and symptoms of injection reactions including hypersensitivity.
For the first 6 doses, patients should be observed during the injection and for 1 hour after for signs and symptoms of injection reactions including hypersensitivity. After that, regardless of the route of administration, the 1-hour post-injection observation time may be reduced or removed according to clinical judgement if the patients have not experienced any injection reactions.
Tysabri 150 mg solution for injection in pre-filled syringe is not intended for intravenous infusion and should be administered via subcutaneous injection only.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Progressive multifocal leukoencephalopathy (PML).

Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies (see sections 4.4 and 4.8).

Combination with other DMTs.

Known active malignancies, except for patients with cutaneous basal cell carcinoma.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and batch number of the administered product should be clearly recorded.

Progressive Multifocal Leukoencephalopathy (PML)

Use of this medicinal product has been associated with an increased risk of PML, an opportunistic infection caused by JC virus, which may be fatal or result in severe disability. Due to this increased risk of developing PML, the benefits and risks of treatment should be individually reconsidered by the specialist physician and the patient; patients must be monitored at regular intervals throughout and should be instructed together with their caregivers on early signs and symptoms of PML. JC virus also causes JCV granule cell neuronopathy (GCN) which has been reported in patients treated with this medicinal product. Symptoms of JCV GCN are similar to symptoms of PML (i.e. cerebellar syndrome).

The following risk factors are associated with an increased risk of PML.

- The presence of anti-JCV antibodies.
- Treatment duration, especially beyond 2 years. After 2 years all patients should be re-informed about the risk of PML with the medicinal product.
- Immunosuppressant use prior to receiving the medicinal product.

Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared to patients who are anti-JCV antibody negative. Patients who have all three risk factors for PML (i.e., are anti-JCV antibody positive **and** have received more than 2 years of therapy with this medicinal product **and** have received prior immunosuppressant therapy) have a significantly higher risk of PML.

In anti-JCV antibody positive natalizumab treated patients who have not used prior immunosuppressants the level of anti-JCV antibody response (index) is associated with the level of risk for PML.

In anti-JCV antibody positive patients, extended interval dosing of natalizumab (average dosing interval of approximately 6 weeks) is suggested to be associated with a lower PML risk compared to approved dosing. If utilising extended interval dosing, caution is required because the efficacy of extended interval dosing has not been established and the associated benefit risk balance is currently unknown (see section 5.1). The decrease in PML risk is based on data from intravenous route of administration. No clinical data are available on either the safety or efficacy of this extended interval dosing with subcutaneous route of administration. For further information, refer to the Physician Information and Management Guidelines.

Patients considered at high risk treatment with this treatment should only be continued if the benefits outweigh the risks. For the estimation of PML risk in the different patient subgroups, please refer to the Physician Information and Management Guidelines.

Anti-JCV antibody testing

Anti-JCV antibody testing provides supportive information for risk stratification of treatment with this medicinal product. Testing for serum anti-JCV antibody prior to initiating therapy or in patients receiving the medicinal product with an unknown antibody status is recommended. Anti-JCV antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result. Re-testing of anti-JCV antibody negative patients every 6 months is recommended. Retesting low index patients who have no history of prior immunosuppressant use every 6 months once they reach the 2 year treatment point is recommended.

The anti-JCV antibody assay (ELISA) should not be used to diagnose PML. Use of plasmapheresis/plasma exchange (PLEX) or intravenous immunoglobulin (IVIg) can affect meaningful interpretation of serum anti-JCV antibody testing. Patients should not be tested for anti-JCV antibodies within 2 weeks of PLEX due to removal of antibodies from the serum, or within 6 months of IVIg (i.e. 6 months = 5x half-life for immunoglobulins).

For further information on anti-JCV antibody testing please see Physician Information and Management Guidelines.

MRI screening for PML

Before initiation of treatment with this medicinal product, a recent (usually within 3 months) MRI should be available as a reference, and be repeated at least on a yearly basis. More frequent MRIs (e.g. on a 3 to 6 monthly basis) using an abbreviated protocol should be considered for patients at higher risk of PML. This includes:

- Patients who have all three risk factors for PML (i.e., are anti-JCV antibody positive **and** have received more than 2 years of therapy with this medicinal product **and** have received prior immunosuppressant therapy),

or

- Patients with a high anti-JCV antibody index who have received more than 2 years of therapy with this medicinal product and without prior history of immunosuppressant therapy.

Current evidence suggests that the risk of PML is low at an index equal to or below 0.9 and increases substantially above 1.5 for patients who have been on treatment with this medicinal product for longer than 2 years (see the Physician Information and Management Guidelines for further information).

No studies have been performed to evaluate the efficacy and safety of this medicinal product when switching patients from DMTs with an immunosuppressant effect. It is unknown if patients switching from these therapies to this treatment have an increased risk of PML, therefore these patients should be monitored more frequently (i.e. similarly to patients switching from immunosuppressants to this medicinal product).

PML should be considered as a differential diagnosis in any MS patient taking natalizumab presenting with neurological symptoms and/or new brain lesions in MRI. Cases of asymptomatic PML based on MRI and positive JCV DNA in the cerebrospinal fluid have been reported.

Physicians should refer to the Physician Information and Management Guidelines for further information on managing the risk of PML in natalizumab-treated patients.

If PML or JCV GCN is suspected, further dosing must be suspended until PML has been excluded.

The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction and, if so, whether these symptoms are typical of MS or possibly suggestive of PML or JCV GCN. If any doubt exists, further evaluation, including MRI scan preferably with contrast (compared with pre-treatment baseline MRI), CSF testing for JC Viral DNA and repeat neurological assessments, should be considered as described in the Physician Information and Management Guidelines (see Educational guidance). Once the clinician has excluded PML and/or JCV GCN (if necessary, by repeating clinical, imaging and/or laboratory investigations if clinical suspicion remains), dosing may resume.

The physician should be particularly alert to symptoms suggestive of PML or JCV GCN that the patient may not notice (e.g. cognitive, psychiatric symptoms or cerebellar syndrome). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

PML has been reported following discontinuation of this medicinal product in patients who did not have findings suggestive of PML at the time of discontinuation. Patients and physicians should continue to follow the same monitoring protocol and be alert for any new signs or symptoms that may be suggestive of PML for approximately 6 months following discontinuation of natalizumab.

If a patient develops PML the dosing of this medicinal product must be permanently discontinued.

Following reconstitution of the immune system in immunocompromised patients with PML improved outcome has been seen.

Based on a retrospective analysis of natalizumab-treated patients, no difference was observed on 2-year survival after PML diagnosis between patients who received PLEX and those who did not. For other considerations on the management of PML, see the Physician Information and Management Guidelines.

<u>PML and IRIS (Immune Reconstitution Inflammatory Syndrome)</u>

IRIS occurs in almost all PML patients treated with this medicinal product after withdrawal or removal of the medicinal product. IRIS is thought to result from the restoration of immune function in patients with PML, which can lead to serious neurological complications and may be fatal. Monitoring for development of IRIS and appropriate treatment of the associated inflammation during recovery from PML should be undertaken (see the Physician Information and Management Guidelines for further information).

Infections including other opportunistic infections

Other opportunistic infections have been reported with use of this medicinal product, primarily in patients with Crohn's disease who were immunocompromised or where significant comorbidity existed, however increased risk of other opportunistic infections with use of the medicinal product in patients without these co-morbidities cannot currently be excluded. Opportunistic infections were also detected in MS patients treated with this medicinal product as a monotherapy (see section 4.8).

This treatment increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses. Serious, life-threatening, and sometimes fatal cases have been reported in the postmarketing setting in multiple sclerosis patients receiving the treatment (see section 4.8). If herpes encephalitis or meningitis occurs, the medicinal product should be discontinued, and appropriate treatment for herpes encephalitis or meningitis should be administered.

Acute retinal necrosis (ARN) is a rare fulminant viral infection of the retina caused by the family of herpes viruses (e.g. varicella zoster). ARN has been observed in patients being administered this medicinal product and can be potentially blinding. Patients presenting with eye symptoms such as decreased visual acuity, redness and painful eye should be referred for retinal screening for ARN. Following clinical diagnosis of ARN, discontinuation of this medicinal product should be considered in these patients.

Prescribers should be aware of the possibility that other opportunistic infections may occur during therapy and should include them in the differential diagnosis of infections that occur in Tysabri-treated patients. If an opportunistic infection is suspected, dosing is to be suspended until such infections can be excluded through further evaluations.

If a patient receiving this medicinal product develops an opportunistic infection, dosing of the medicinal product must be permanently discontinued.

Educational guidance

All physicians who intend to prescribe the medicinal product must ensure they are familiar with the Physician Information and Management Guidelines.

Physicians must discuss the benefits and risks of natalizumab therapy with the patient and provide them with a patient alert card. Patients should be instructed that if they develop any infection then they should inform their physician that they are being treated with this medicinal product.

Physicians should counsel patients on the importance of uninterrupted dosing, particularly in the early months of treatment (see hypersensitivity).

Hypersensitivity

Hypersensitivity reactions have been associated with this medicinal product, including, for the intravenous infusion, serious systemic reactions (see section 4.8).

These reactions usually occurred within one hour after administration. The risk for hypersensitivity was greatest with early infusions and in patients re-exposed to treatment following an initial short exposure (one or two infusions) and extended period (three months or more) without treatment. However, the risk of hypersensitivity reactions should be considered for every administration.

Patients are to be observed during the subcutaneous injections and for 1 hour after, for signs and symptoms of injection reactions including hypersensitivity (see sections 4.2 and 4.8). Resources for the management of hypersensitivity reactions should be available.

This medicinal product should be discontinued and appropriate therapy initiated at the first symptoms or signs of hypersensitivity.

Patients who have experienced a hypersensitivity reaction must be permanently discontinued from treatment with natalizumab.

There are limited data for the subcutaneous formulation in the Tysabri naïve patient population (see section 5.1).

Concurrent treatment with immunosuppressants

The safety and efficacy of this medicinal product in combination with other immunosuppressive and antineoplastic therapies have not been fully established. Concurrent use of these agents with this medicinal product may increase the risk of infections, including opportunistic infections, and is contraindicated (see section 4.3).

In phase 3 MS clinical trials with natalizumab intravenous infusion, concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection. Short courses of corticosteroids can be used in combination with this medicinal product.

Prior treatment with immunosuppressive or immunomodulatory therapies

Patients with a treatment history of immunosuppressant medications are at increased risk for PML.
No studies have been performed to evaluate the efficacy and safety of the medicinal product when switching patients from DMTs with an immunosuppressant effect. It is unknown if patients switching from these therapies to this medicinal product have an increased risk of PML, therefore these patients should be monitored more frequently (i.e. similarly to patients switching from immunosuppressants to this medicinal product, see MRI screening for PML).

Care should be taken with patients who have previously received immunosuppressants to allow sufficient time for immune function recovery to occur. Physicians must evaluate each individual case to determine whether there is evidence of an immunocompromised state prior to commencing treatment (see section 4.3).

When switching patients from another DMT to this medicinal product, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation. A Complete Blood Count (CBC, including lymphocytes) is recommended prior to initiating treatment to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved.

Patients can switch directly from beta interferon or glatiramer acetate to natalizumabt providing there are no signs of relevant treatment-related abnormalities e.g. neutropenia and, lymphopenia.

When switching from dimethyl fumarate, the washout period should be sufficient for lymphocyte count to recover before treatment is started.

Following discontinuation of fingolimod, lymphocyte count progressively returns to normal range within 1 to 2 months after stopping therapy. The washout period should be sufficient for lymphocyte count to recover before treatment is started.

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, clearance of teriflunomide from plasma can take from several months up to 2 years. An accelerated elimination procedure as defined in the teriflunomide Summary of Product Characteristics is recommended or alternatively washout period should not be shorter than 3.5 months. Caution regarding potential concomitant immune effects is required when switching patients from teriflunomide to this medicinal product.

Alemtuzumab has profound prolonged immunosuppressive effects. As the actual duration of these effects is unknown, initiating treatment with this medicinal product after alemtuzumab is not recommended unless the benefits clearly outweigh the risks for the individual patient.

Immunogenicity

Disease exacerbations or injection related events may indicate the development of antibodies against natalizumab. In these cases the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after at least 6 weeks, treatment should be discontinued, as persistent antibodies are associated with a substantial decrease in efficacy of this medicinal product and an increased incidence of hypersensitivity reactions (see section 4.8).

Since patients who have received an initial short exposure to this medicinal product and then had an extended period without treatment are at a higher risk of developing anti-natalizumab antibodies and/or hypersensitivity upon redosing, the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after at least 6 weeks, the patient should not receive further treatment with natalizumab (see section 5.1).

Hepatic events

Spontaneous serious adverse reactions of liver injury have been reported during the post-marketing phase (see section 4.8). These liver injuries may occur at any time during treatment, even after the first dose. In some instances, the reaction reoccurred when treatment was reintroduced. Some patients with a past medical history of an abnormal liver test have experienced an exacerbation of abnormal liver test while on treatment. Patients should be

monitored as appropriate for impaired liver function, and be instructed to contact their physician in case signs and symptoms suggestive of liver injury occur, such as jaundice and vomiting. In cases of significant liver injury this medicinal product should be discontinued.

Stopping therapy

If a decision is made to stop treatment with natalizumab, the physician needs to be aware that natalizumab remains in the blood, and has pharmacodynamic effects (e.g increased lymphocyte counts) for approximately 12 weeks following the last dose. Starting other therapies during this interval will result in a concomitant exposure to natalizumab. For medicinal products such as interferon and glatiramer acetate, concomitant exposure of this duration was not associated with safety risks in clinical trials. No data are available in MS patients regarding concomitant exposure with immunosuppressant medication. Use of these medicinal products soon after the discontinuation of natalizumab may lead to an additive immunosuppressive effect. This should be carefully considered on a case-by-case basis, and a wash-out period of natalizumab might be appropriate. Short courses of steroids used to treat relapses were not associated with increased infections in clinical trials.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose (300 mg natalizumab), that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Natalizumab is contraindicated in combination with other DMTs (see section 4.3).

Immunisations

In a randomised, open label study of 60 patients with relapsing MS there was no significant difference in the humoral immune response to a recall antigen (tetanus toxoid) and only slightly slower and reduced humoral immune response to a neoantigen (keyhole limpet haemocyanin) was observed in patients who were treated with this medicinal product for 6 months compared to an untreated control group. Live vaccines have not been studied.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

If a woman becomes pregnant while taking this medicinal product, discontinuation of treatment should be considered. A benefit-risk evaluation of the use of this medicinal product during pregnancy should take into account the patient's clinical condition and the possible return of disease activity after stopping the medicinal product.

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3).

Data from clinical trials, a prospective pregnancy registry, post-marketing cases and available

literature do not suggest an effect of this medicinal product exposure on pregnancy outcomes.

The completed prospective Tysabri pregnancy registry contained 355 pregnancies with available outcomes. There were 316 live births, 29 of which were reported to have birth defects. Sixteen of the 29 were classified as major defects. The rate of defects corresponds to the defect rates reported in other pregnancy registries involving MS patients. There is no evidence of a specific pattern of birth defects with this medicinal product.

Cases from published literature reported transient mild to moderate thrombocytopenia and anaemia observed in infants born to women exposed to natalizumab in their third trimester of pregnancy. Therefore, it is recommended that newborns of women exposed to the medicinal product during the third trimester of pregnancy are monitored for potential haematological abnormalities.

Breast-feeding

Natalizumab is excreted in human milk. The effect of natalizumab on newborn/infants is unknown. Breast-feeding should be discontinued during treatment with natalizumabt.

Fertility

Reductions in female guinea pig fertility were observed in one study at doses in excess of the human dose; natalizumab did not affect male fertility. It is considered unlikely that natalizumab will affect fertility performance in humans following the maximum recommended dose.

4.7 Effects on ability to drive and use machines

Tysabri has a minor influence on the ability to drive and use machines. Dizziness may occur following administration of natalizumab (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety profile observed for natalizumab administered subcutaneously was consistent with the known safety profile of natalizumab administered intravenously, with the exception of injection site pain. The overall frequency of injection site pain was common 4% (3/71) for subjects receiving natalizumab 300 mg, every 4 weeks, by subcutaneous administration.

In placebo-controlled trials in 1,617 MS patients treated with natalizumab (intravenous infusion), for up to 2 years (placebo: 1,135), adverse events leading to discontinuation of therapy occurred in 5.8% of patients treated with natalizumab (placebo: 4.8%). Over the 2-year duration of the studies, 43.5% of patients treated with natalizumab reported adverse reactions (placebo: 39.6%).

In clinical trials in 6786 patients treated with natalizumab (intravenous infusion and subcutaneous injection), the most frequently occurring adverse reactions were headache (32%), nasopharyngitis (27%), fatigue (23%), urinary tract infection (16%), nausea (15%), arthralgia (14%), and dizziness (11%) associated with natalizumab administration.

Tabulated list of adverse reactions

Adverse reactions arising from clinical studies, post-authorisation safety studies and spontaneous reports are presented in Table 1 below. Within the system organ classes they are listed under the following headings: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions

MedDRA System Organ Class	Frequency of adverse reactions				
	Very Common	*Common*	*Uncommon*	*Rare*	*Not known*
Infections and infestations	Nasopharyngitis Urinary tract infection	Herpes infection	Progressive multifocal leukoencephalopathy	Herpes ophthalmic	Meningoencephalitis herpetic JC virus granule cell neuropathy Necrotising herpetic retinopathy
Immune system disorders		Hypersensitivity	Anaphylactic reaction Immune reconstitution inflammatory syndrome		
Blood and lymphatic system disorders		Anaemia	Eosinophilia	Haemolytic anaemia Nucleated red cells	
Hepatobiliary disorders				Hyperbilirubinaemia	Liver injury
Investigations		Hepatic enzyme increased Drug specific antibody present			
Injury, poisoning and procedural complications	Infusion related reaction				
Respiratory, thoracic and mediastinal disorders		Dyspnoea			
Gastrointestinal disorders	Nausea	Vomiting			
General disorders and administration site conditions	Fatigue	Pyrexia Chills Infusion site reaction Injection site reaction	Face oedema		

MedDRA System Organ Class	Frequency of adverse reactions				
	Very Common	*Common*	*Uncommon*	*Rare*	*Not known*
Skin and subcutaneous tissue disorders		Pruritus Rash Urticaria		Angioedema	
Vascular disorders		Flushing			
Nervous system disorders	Dizziness Headache				
Musculoskeletal and connective tissue disorders	Arthralgia				

Description of selected adverse reactions

Hypersensitivity reactions

Hypersensitivity reactions usually occurred within one hour after completion of the subcutaneous injections. The number of patients analysed in the DELIVER and REFINE studies was low (see section 5.1).

In 2-year controlled clinical trials in MS patients receiving natalizumab intravenously, hypersensitivity reactions occurred in up to 4% of patients. Anaphylactic/anaphylactoid reactions occurred in less than 1% of patients receiving this medicinal product. Hypersensitivity reactions usually occurred during the infusion or within the 1-hour period after the completion of the infusion (see section 4.4). In post-marketing experience, there have been reports of hypersensitivity reactions which have occurred with one or more of the following associated symptoms: hypotension, hypertension, chest pain, chest discomfort, dyspnoea, angioedema, in addition to more usual symptoms such as rash and urticaria.

Immunogenicity

In 10% of patients antibodies against natalizumab were detected in 2-year controlled clinical trials in MS patients receiving natalizumab intravenously. Persistent anti-natalizumab antibodies (one positive test reproducible on retesting at least 6 weeks later) developed in approximately 6% of patients. Antibodies were detected on only one occasion in an additional 4% of patients. Persistent antibodies were associated with a substantial decrease in the effectiveness of natalizumab and an increased incidence of hypersensitivity reactions. Additional infusion-related reactions associated with persistent antibodies included rigors, nausea, vomiting and flushing (see section 4.4). In the 32-week DELIVER study in MS patients with no prior exposure to natalizumab, persistent anti-natalizumab antibodies developed in 1 subject (4%) from 26 subjects who received natalizumab subcutaneously. Antibodies were detected on only one occasion in another 5 subjects (19%). In the 60-week REFINE study in MS patients, no subjects (136 subjects) who switched from natalizumab intravenous administration to subcutaneous administration had detectable ADA during the study (see section 5.1).

If, after approximately 6 months of therapy, persistent antibodies are suspected, either due to reduced efficacy or due to occurrence of infusion-related events, they may be detected and confirmed with a subsequent test 6 weeks after the first positive test. Given that efficacy may

be reduced or the incidence of hypersensitivity or infusion-related reactions may be increased in a patient with persistent antibodies, treatment should be discontinued in patients who develop persistent antibodies.

Infections, including PML and opportunistic infections

In 2-year controlled clinical trials in MS patients, the rate of infection was approximately 1.5 per patient-year in both natalizumab (intravenously)- and placebo-treated patients. The nature of the infections was generally similar in natalizumab- and placebo-treated patients. A case of *cryptosporidium* diarrhoea was reported in MS clinical trials. In other clinical trials, cases of additional opportunistic infections have been reported, some of which were fatal. The majority of patients did not interrupt natalizumab therapy during infections and recovery occurred with appropriate treatment.

In clinical trials (intravenous formulation), herpes infections (Varicella-Zoster virus, Herpes-simplex virus) occurred slightly more frequently in natalizumab-treated patients than in placebo-treated patients. In post-marketing experience, serious, life-threatening, and sometimes fatal cases of encephalitis and meningitis caused by herpes simplex or varicella zoster have been reported in multiple sclerosis patients receiving natalizumab. The duration of treatment with natalizumab prior to onset ranged from a few months to several years (see section 4.4).

In postmarketing experience, rare cases of ARN have been observed in patients receiving this medicinal product. Some cases have occurred in patients with central nervous system (CNS) herpes infections (e.g. herpes meningitis and encephalitis). Serious cases of ARN, either affecting one or both eyes, led to blindness in some patients. The treatment reported in these cases included anti-viral therapy and in some cases, surgery (see section 4.4).

Cases of PML have been reported from clinical trials, post-marketing observational studies and post-marketing passive surveillance. PML usually leads to severe disability or death (see section 4.4). Cases of JCV GCN have also been reported during postmarketing use of this medicinal product Symptoms of JCV GCN are similar to PML.

Hepatic events

Spontaneous cases of serious liver injuries, increased liver enzymes, hyperbilirubinaemia have been reported during the post-marketing phase (see section 4.4).

Anaemia and haemolytic anaemia

Rare, serious cases of anaemia and haemolytic anaemia have been reported in patients treated with natalizumab in post-marketing observational studies.

Malignancies

No differences in incidence rates or the nature of malignancies between natalizumab- and placebo-treated patients were observed over 2 years of treatment. However, observation over longer treatment periods is required before any effect of natalizumab on malignancies can be excluded (see section 4.3).

Effects on laboratory tests

In 2-year controlled clinical trials in MS patients treatment with natalizumab was associated with increases in circulating lymphocytes, monocytes, eosinophils, basophils and nucleated red blood cells. Elevations in neutrophils were not seen. Increases from baseline for lymphocytes, monocytes, eosinophils and basophils ranged from 35% to 140% for individual cell types but mean cell counts remained within normal ranges with intravenous infusion administration. During treatment with this medicinal product, small reductions in haemoglobin (mean decrease 0.6 g/dL), haematocrit (mean decrease 2%) and red blood cell counts (mean decrease 0.1 x 10^6/L) were seen. All changes in haematological variables returned to pre-treatment values, usually within 16 weeks of last dose of the medicinal product and the changes were not associated with clinical symptoms. In post-marketing experience, there have also been reports of eosinophilia (eosinophil count >1,500/mm^3) without clinical symptoms. In such cases where therapy was discontinued the elevated eosinophil levels resolved.

Paediatric population

Serious adverse events were evaluated in 621 MS paediatric patients included in a meta-analysis (see also section 5.1). Within the limitations of these data, there were no new safety signals identified in this patient population. 1 case of herpes meningitis was reported in the meta-analysis. No cases of PML were identified in the meta-analysis, however, PML has been reported in natalizumab-treated paediatric patients in the post-marketing setting.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

Malta
ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

United Kingdom (Northern Ireland)
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Safety of doses higher than 300 mg has not been adequately evaluated. The maximum amount of natalizumab that can be safely administered has not been determined.

There is no known antidote for natalizumab overdose. Treatment consists of discontinuation of the medicinal product and supportive therapy as needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA23

Pharmacodynamic effects

Natalizumab is a selective adhesion-molecule inhibitor and binds to the α4-subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the α4β1 integrin, blocking the interaction with its cognate receptor, vascular cell adhesion molecule-1 (VCAM-1), and ligands osteopontin, and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). Natalizumab blocks the interaction of α4β7 integrin with the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site, and inhibit further recruitment of immune cells into inflamed tissues.

In MS, lesions are believed to occur when activated T-lymphocytes cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and endothelial cells of the vessel wall. The interaction between α4β1 and its targets is an important component of pathological inflammation in the brain and disruption of these interactions leads to reduced inflammation. Under normal conditions, VCAM-1 is not expressed in the brain parenchyma. However, in the presence of pro-inflammatory cytokines, VCAM-1 is upregulated on endothelial cells and possibly on glial cells near the sites of inflammation. In the setting of central nervous system (CNS) inflammation in MS, it is the interaction of α4β1 with VCAM-1, CS-1 and osteopontin that mediates the firm adhesion and transmigration of leukocytes into the brain parenchyma and may perpetuate the inflammatory cascade in CNS tissue. Blockade of the molecular interactions of α4β1 with its targets reduces inflammatory activity present in the brain in MS and inhibits further recruitment of immune cells into inflamed tissue, thus reducing the formation or enlargement of MS lesions.

Based on PK/α4β1 integrin binding relationships established in the updated population pharmacokinetic/pharmacodymanic model, the EC50 of natalizumab binding to α4β1 integrin is estimated to be 2.5 mg/L. There was no difference in α4β1integrin binding after natalizumab 300 mg every 4 weeks was administered subcutaneously or intravenously.

Clinical efficacy

Based on similarities in pharmacokinetics and pharmacodynamics between intravenous and subcutaneous administration, the efficacy data from intravenous infusion is provided as well as those from patients receiving the subcutaneous injection.

AFFIRM clinical study

Efficacy as monotherapy for intravenous infusion has been evaluated in one randomised, double-blind, placebo-controlled study lasting 2 years (AFFIRM study) in RRMS patients who had experienced at least 1 clinical relapse during the year prior to entry and had a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5. Median age was 37 years, with a median disease duration of 5 years. The patients were randomised with a 2:1 ratio to receive natalizumab 300 mg (n = 627) or placebo (n = 315) every 4 weeks for up to 30 infusions. Neurological evaluations were performed every 12 weeks and at times of suspected relapse. MRI evaluations for T1-weighted gadolinium (Gd)-enhancing lesions and T2-hyperintense lesions were performed annually.

Study features and results are presented in the Table 2.

Table 2. AFFIRM study: Main features and results		
Design	Monotherapy; randomised double-blind placebo-controlled parallel-group trial for 120 weeks	
Subjects	RRMS (McDonald criteria)	
Treatment	Placebo / Natalizumab 300 mg i.v. every 4 weeks	
One year endpoint	Relapse rate	
Two year endpoint	Progression on EDSS	
Secondary endpoints	Relapse rate derived variables / MRI-derived variables	
Subjects	Placebo	Natalizumab
Randomised	315	627
Completing 1 years	296	609
Completing 2 years	285	589
Age yrs, median (range)	37 (19-50)	36 (18-50)
MS-history yrs, median (range)	6.0 (0-33)	5.0 (0-34)
Time since diagnosis, yrs median (range)	2.0 (0-23)	2.0 (0-24)
Relapses in previous 12 months, median (range)	1.0 (0-5)	1.0 (0-12)
EDSS-baseline, median (range)	2 (0-6.0)	2 (0-6.0)
RESULTS		
Annual relapse rate		
After one year (primary endpoint)	0.805	0.261
After two years	0.733	0.235
One year	Rate ratio 0.33 $CI_{95\%}$ 0.26 ; 0.41	
Two years	Rate ratio 0.32 $CI_{95\%}$ 0.26 ; 0.40	
Relapse free		
After one year	53%	76%
After two years	41%	67%
Disability		
Proportion progressed[1](12-week confirmation; primary outcome)	29%	17%

Table 2. AFFIRM study: Main features and results		
Design	Monotherapy; randomised double-blind placebo-controlled parallel-group trial for 120 weeks	
	Hazard ratio 0.58, $CI_{95\%}$ 0.43; 0.73, p<0.001	
Proportion progressed[1](24-week confirmation)	23%	11%
	Hazard ratio 0.46, $CI_{95\%}$ 0.33; 0.64, p<0.001	
MRI (0-2 years)		
Median % change in T2-hyperintense lesion volume	+8.8%	-9.4% (p<0.001)
Mean number of new or newly-enlarging T2-hyperintense lesions	11.0	1.9 (p<0.001)
Mean number of T1-hypointense lesions	4.6	1.1 (p<0.001)
Mean number of Gd-enhancing lesions	1.2	0.1 (p<0.001)

[1] Progression of disability was defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 12 or 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS =0 sustained for 12 or 24 weeks.

In the sub-group of patients indicated for treatment of rapidly evolving RRMS (patients with 2 or more relapses and 1 or more Gd+ lesion), the annualised relapse rate was 0.282 in the natalizumab-treated group (n = 148) and 1.455 in the placebo group (n = 61) (p < 0.001). Hazard ratio for disability progression was 0.36 (95% CI: 0.17, 0.76) p = 0.008. These results were obtained from a *post hoc* analysis and should be interpreted cautiously. No information on the severity of the relapses before inclusion of patients in the study is available.

Tysabri Observational Program (TOP)

Interim analysis of results (as of May 2015) from the ongoing Tysabri Observational Program (TOP), a phase 4, multicentre, single-arm study (n = 5,770) demonstrated that patients switching from beta interferon (n= 3,255) or glatiramer acetate (n = 1,384) to Tysabri showed a sustained, significant decrease in annualised relapse rate (p < 0.0001). Mean EDSS scores remained stable over 5 years. Consistent with efficacy results observed for patients switching from beta interferon or glatiramer acetate to Tysabri, for patients switching from fingolimod (n = 147) to this medicinal product, a significant decrease in annualised relapse rate (ARR) was observed, which remained stable over 2 years, and mean EDSS scores remained similar from baseline to Year 2. The limited sample size and shorter duration of natalizumab exposure for this subgroup of patients should be considered when interpreting these data.

Paediatric population

A post-marketing meta-analysis was conducted using data from 621 paediatric MS patients treated with natalizumab (median age 17 years, range was 7 to 18 years, 91% aged ≥14 years). Within this analysis, a limited subset of patients with data available prior to treatment (158 of the 621 patients) demonstrated a reduction in ARR from 1.466 (95% CI 1.337, 1.604) prior to treatment to 0.110 (95% CI 0.094, 0.128).

Extended interval dosing

In a pre-specified, retrospective analysis of US anti-JCV antibody positive Tysabri patients intravenously administered (TOUCH registry), the risk of PML was compared between patients treated with the approved dosing interval and patients treated with extended interval dosing as identified in the last 18 months of exposure (EID, average dosing intervals of approximately 6 weeks). The majority (85%) of patients dosed with EID had received the approved dosing for ≥1 year prior to switching to EID. The interim analysis showed a lower risk of PML in patients treated with EID (hazard ratio = 0.06, 95% CI of hazard ratio = 0.01 to 0.22). The efficacy of this medicinal product when administered with EID has not been established, and therefore the benefit/risk balance of EID is unknown (see section 4.4).

Efficacy has been modelled for patients who switch to longer dosing after ≥1 year of approved dosing with this medicinal product under intravenous administration and who did not experience a relapse in the year prior to switching. Current pharmacokinetic/pharmacodynamic statistical modelling and simulation indicate that the risk of MS disease activity for patients switching to longer dosing intervals may be higher for patients with body weight >80kg or those with dosing intervals ≥7 weeks. No prospective clinical studies have been completed to validate these findings.

No clinical data are available on either the safety or efficacy of this extended interval dosing with the subcutaneous route of administration.

REFINE clinical study (subcutaneous formulation, population pre-treated with natalizumab [intravenous infusion] for a minimum of 12 months)

Subcutaneous administration was assessed in a randomised, blinded, parallel-group, phase 2 study (REFINE) exploring the safety, tolerability, and efficacy of multiple regimens of natalizumab (300 mg intravenous every 4 weeks, 300 mg subcutaneous every 4 weeks, 300 mg intravenous every 12 weeks, 300 mg subcutaneous every 12 weeks, 150 mg intravenous every 12 weeks and 150 mg subcutaneous every 12 weeks) in adult subjects (n=290) with relapsing remitting multiple sclerosis conducted over a 60 week period. Subjects had received natalizumab for at least 12 months and were free from replapse for 12 months prior to randomisation. The primary objective of this study was to explore the effects of multiple regimens of natalizumab on disease activity and safety in subjects with RRMS.The primary endpoint of this study was the cumulative number of combined unique active (CUA) MRI lesions (sum of new Gd+ lesions on brain MRI and new or newly enlarging T2 hyperintense lesions not associated with Gd+ on T1 weighted scans). The mean CUA for the 300 mg subcutaneous every 4 week arm was low (0.02) and comparable to the 300 mg intravenous every 4 weeks arm (0.23). The CUA in the every 12 week treatment arms was significantly higher than the every 4 week treatment arms resulting in the early discontinuation of the every 12 week arms. Due to the exploratory nature of this study, no formal efficacy comparisons were made.

DELIVER clinical study (subcutaneous formulation, natalizumab naïve population)

The efficacy and safety of natalizumab for subcutaneous administration in the natalizumab naïve MS population was evaluated in a phase 1 randomised, open-label, dose-ranging study (DELIVER). 12 subjects with RRMS and 14 subjects with secondary progressive MS were enrolled in the subcutaneous treatment arms. The study's primary objective was to compare the pharmacokinetics (PK) and pharmacodynamics (PD) of single subcutaneous or intramuscular 300-mg doses of natalizumab with intravenous infusion 300-mg doses of natalizumab in patients with multiple sclerosis (MS). Secondary objectives included

investigation of the safety, tolerability, and immunogenicity of repeated subcutaneous and intramuscular natalizumab doses. An exploratory endpoint of this study included the number of new Gd+ lesions on brain MRI from baseline to Week 32. None of the subjects treated with natalizumab had any Gd+ lesions post-baseline, regardless of their disease stage (RRMS or secondary progressive MS), assigned route of administration, or the presence of Gd+ lesions at baseline. Across the RRMS and secondary progressive MS populations, 2 patients in the natalizumab 300 mg subcutaneous group experienced relapses compared to 3 patients in the natalizumab 300 mg intravenous infusion group. Small sample sizes and inter- and intra-patient variability prevent meaningful comparisons of efficacy data between groups.

5.2 Pharmacokinetic properties

The pharmacokinetics of natalizumab after subcutaneous administration was evaluated in 2 studies. DELIVER was a phase 1, randomised, open-label, dose-ranging study to evaluate the pharmacokinetics of subcutaneous and intramuscular natalizumab in subjects with MS (RRMS or secondary progressive MS) (n = 76). (see section 5.1 for a description of the REFINE study).

An updated population pharmacokinetic analysis was conducted consisting of 11 studies (conducted with subcutaneously and intravenously administered natalizumab) and data with serial PK sampling as measured by an industry standard assay. It included over 1,286 subjects receiving doses ranging from 1 to 6 mg/kg and fixed doses of 150/ 300 mg.

Absorption

The absorption from the injection site to systemic circulation following SC administration was characterised by first order absorption with a model estimated delay of 3 hours. No covariates were identified.

The bioavailability of natalizumab after subcutaneous administration was 82% as estimated using the updated population pharmacokinetic analysis. After SC administration of 300 mg natalizumab, peak values (Cmax) were reached by approximately 1 week (tmax: 5.8 days, range from 2 to 7.9 days).

The mean Cmax for RRMS participants was 35.44 μg/mL (range 22.0 to 47.8 μg/mL) being 33% of the peak values achieved following IV administration.

Multiple subcutaneous doses of 300 mg administered every 4 weeks resulted in comparable C_{trough} to 300 mg administered intravenously every 4 weeks. The predicted time to steady-state was approximately 24 weeks. In both intravenous and subcutaneous administration of natalizumab (every 4 weeks) C_{trough} values resulted in comparable α4β1 integrin binding.

Distribution

Both intravenous and subcutaneous routes of administration shared the same disposition PK parameters (CL, V_{ss} and $t_{½}$) and same sets of covariates as described in the updated population pharmacokinetic analysis.

Median steady-state volume of distribution was 5.58 L (5.27-5.92 L, 95% confidence interval).

Elimination

Population median estimate for linear clearance was 6.21 mL/h (5.60-6.70 mL/h, 95% confidence interval) and the estimated median half-life was 26.8 days. The 95th percentile interval of the terminal half-life is from 11.6 to 46.2 days.

The population analysis of 1,286 patients explored the effects of selected covariates including body weight, age, gender, presence of anti-natalizumab antibodies and formulation on pharmacokinetics. Only body weight, the presence of anti-natalizumab antibodies and the formulation used in phase 2 studies were found to influence natalizumab disposition. Natalizumab clearance increased with body weight in a less than proportional manner, such that a +/-43% change in body weight resulted in only a -38% to 36% change in clearance. The presence of persistent anti-natalizumab antibodies increased natalizumab clearance approximately 2.54-fold, consistent with reduced serum natalizumab concentrations observed in persistently antibody-positive patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Consistent with the pharmacological activity of natalizumab, altered trafficking of lymphocytes was seen as white blood cell increases as well as increased spleen weights in most *in vivo* studies. These changes were reversible and did not appear to have any adverse toxicological consequences.

In studies conducted in mice, growth and metastasis of melanoma and lymphoblastic leukaemia tumour cells was not increased by the administration of natalizumab.

No clastogenic or mutagenic effects of natalizumab were observed in the Ames or human chromosomal aberration assays. Natalizumab showed no effects on *in vitro* assays of α4-integrin-positive tumour line proliferation or cytotoxicity.

Reductions in female guinea pig fertility were observed in one study at doses in excess of the human dose; natalizumab did not affect male fertility.

The effect of natalizumab on reproduction was evaluated in 5 studies, 3 in guinea pigs and 2 in *cynomolgus* monkeys. These studies showed no evidence of teratogenic effects or effects on growth of offspring. In one study in guinea pigs, a small reduction in pup survival was noted. In a study in monkeys, the number of abortions was doubled in the natalizumab 30 mg/kg treatment groups versus matching control groups. This was the result of a high incidence of abortions in treated groups in the first cohort that was not observed in the second cohort. No effects on abortion rates were noted in any other study. A study in pregnant *cynomolgus* monkeys demonstrated natalizumab-related changes in the foetus that included mild anaemia, reduced platelet counts, increased spleen weights and reduced liver and thymus weights. These changes were associated with increased splenic extramedullary haematopoiesis, thymic atrophy and decreased hepatic haematopoiesis. Platelet counts were also reduced in offspring born to mothers treated with natalizumab until parturition, however

there was no evidence of anaemia in these offspring. All changes were observed at doses in excess of the human dose and were reversed upon clearance of natalizumab.

In *cynomolgus* monkeys treated with natalizumab until parturition, low levels of natalizumab were detected in the breast milk of some animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate, monobasic, monohydrate
Sodium phosphate, dibasic, heptahydrate
Sodium chloride
Polysorbate 80 (E 433)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2˚C - 8˚C).
Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

The pre-filled syringes (PFS) can be kept in their original packaging for up to 24 hours at room temperature (up to 25^{o} C). The PFS must not be returned to refrigeration. Do not use external heat sources such as hot water to warm the PFS.

6.5 Nature and contents of container

Each PFS consists of a pre-filled syringe made of glass (Type 1A) with a rubber stopper and thermoplastic rigid needle shield, containing 1 mL of solution. A 27 gauge needle is pre-affixed to the syringe. Each PFS has a needle guard system that will automatically cover the exposed needle when the plunger is fully depressed.

Pack size of two PFS per carton.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local
requirements.

7. MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/346/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th March 2021

10. DATE OF REVISION OF THE TEXT

03/2021

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

APPENDIX 2. PACKAGE LEAFLET (PL)

Tysabri 300 mg concentrate for solution for infusion
Tysabri 150 mg solution for injection in pre-filled syringe

Package leaflet: Information for the patient

Tysabri 300 mg concentrate for solution for infusion
natalizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

In addition to this leaflet you will be given a patient alert card. This contains important safety information that you need to know before and during treatment with Tysabri.

- Keep this leaflet and the patient alert card. You may need to read them again. Keep the leaflet and patient alert card with you during treatment and for six months after the last dose of this medicine , as side effects may occur even after you have stopped treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Tysabri is and what it is used for

Tysabri is used to treat multiple sclerosis (MS). It contains the active substance natalizumab. This is called a monoclonal antibody.

MS causes inflammation in the brain that damages the nerve cells. This inflammation happens when white blood cells get into the brain and spinal cord. This medicine stops the white blood cells getting through to the brain. This reduces nerve damage caused by MS.

Symptoms of multiple sclerosis
The symptoms of MS vary from patient to patient, and you may experience some or none of them.

They may include: walking problems, numbness in the face, arms or legs; problems with vision; tiredness; feeling off-balance or light headed; bladder and bowel problems; difficulty in thinking and concentrating; depression; acute or chronic pain; sexual problems; stiffness and muscle spasms.
When the symptoms flare up, it is called a *relapse* (also known as an exacerbation or an attack). When a relapse occurs, you may notice the symptoms suddenly, within a few hours, or slowly progressing over several days. Your symptoms will then usually improve gradually (this is called a remission).

How Tysabri can help
In trials, this medicine approximately halved the build-up of disability caused by MS, and decreased the number of MS attacks by about two-thirds. While you are treated with this medicine you might not notice any improvement, but it may still be working to prevent your MS becoming worse.

2. What you need to know before you receive Tysabri

Before you start treatment with this medicine, it is important that you and your doctor have discussed the benefits you could expect to receive from this treatment and the risks that are associated with it.

You must not be given Tysabri

- If you are **allergic** to natalizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have been **diagnosed with PML** (*progressive multifocal leukoencephalopathy*). PML is an uncommon infection of the brain.
- If your **immune system** has a serious problem with your immune system (This may be due to disease such as HIV) or to a medicine you are taking, or have taken in the past (see below).
- If you are taking **medicines that affect your immune system,** including certain other medicines used to treat MS. These medicines cannot be used with Tysabri.
- If you **have cancer** (unless it is a type of skin cancer called *basal cell carcinoma*).

Warnings and precautions

You need to discuss with your doctor whether Tysabri is the most suitable treatment for you. Do this before you start taking Tysabri, and when you have been receiving Tysabri for more than two years.

Possible brain infection (PML)

Some people receiving this medicine (fewer than 1 in 100) have had an uncommon brain infection called PML (*progressive multifocal leukoencephalopathy*). PML can lead to severe disability or death.

- Before starting treatment, **all patients will have blood tests** arranged by the doctor for JC virus infection. JC virus is a common virus that does not normally make you ill. However, PML is linked to an increase of JC virus in the brain. The reason for this increase in some patients treated with Tysabri is not clear. Before and during treatment, your doctor will test your blood to check if you have antibodies to the JC virus, which are a sign that you have been infected by the JC virus.

- Your doctor will arrange a **Magnetic Resonance Imaging (MRI) scan**, which will be repeated during treatment to rule out PML.

- **The symptoms of PML** may be similar to an MS relapse (see section 4, *Possible side effects*). You can also get PML up to 6 months after stopping Tysabri treatment.

  Tell your doctor as soon as possible if you notice your MS getting worse, if you notice any new symptoms while you are on Tysabri treatment or for up to 6 months afterwards.

- **Tell your partner or caregivers** about what to look out for (see also section 4, *Possible side effects*). Some symptoms might be difficult to spot by yourself, such as changes in mood or behaviour, confusion, speech and communication difficulties. If you get any of these, **you may need further tests**. Keep looking out for symptoms in the 6 months after stopping Tysabri.

- Keep the patient alert card you have been given by your doctor. It includes this information. Show it to your partner or caregivers.

Three things can increase your risk of PML with Tysabri. If you have two or more of these risk factors, the risk is increased further:

- **If you have antibodies to the JC virus** in your blood. These are a sign that the virus is in your body. You will be tested before and during Tysabri treatment.

- **If you are treated for a long time** with Tysabri, especially if it is more than two years.

- **If you have taken a medicine called an *immunosuppressant***, that reduces the activity of your immune system.

Another condition, called JCV GCN (*JC virus granule cell neuronopathy*), is also caused by JC virus and has occurred in some patients receiving Tysabri. The symptoms of JCV GNC are similar to PML.

For those with a lower risk of PML, your doctor may repeat the test regularly to check that:

- You still do not have antibodies to the JC virus in your blood.

- If you have been treated for more than 2 years, you still have a lower level of JC virus antibodies in your blood.

If someone gets PML
PML can be treated, and Tysabri treatment will be stopped. However, some people get a reaction as Tysabri is removed from the body. This reaction (known as IRIS or immune reconstitution inflammatory syndrome) may lead to your condition getting worse, including worsening of brain function.

Look out for other infections
Some infections other than PML may also be serious and can be due to viruses, bacteria, and other causes.

Tell a doctor or nurse immediately if you think you have an infection (see also section 4, *Possible side effects*).

Children and adolescents
Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and Tysabri
Tell your doctor if you are taking, have recently taken or might take any other medicines.

- You **must not** be given this medicine if you are now being treated with medicines that affect your **immune system**, including certain other medicines to treat your MS.

- You might not be able to use this medicine if you have **previously** had any that affect your immune system.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

- **Do not use this medicine if you are pregnant,** unless you have discussed this with your doctor. Be sure to tell your doctor immediately if you get pregnant, think you may be pregnant, or if you are planning to become pregnant.

- **Do not breast-feed whilst using Tysabri.** Your doctor will help you decide whether you should choose to stop breast-feeding or stop using the medicine.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. The risk to the baby and benefit to the mother will be taken into consideration by your doctor.

Driving and using machines
Dizziness is a very common side effect. If you are affected, do not drive or use machines.

Tysabri contains sodium
Each vial of this medicine contains 2.3 mmol (or 52 mg) of sodium. After dilution for use, this medicinal product contains 17.7 mmol (or 406 mg) sodium per dose. This should be considered if you are on a controlled sodium diet.

3. How Tysabri is given

Tysabri IV infusion will be given to you by a doctor experienced in the treatment of MS. Your doctor may switch you directly from another medicine for MS to Tysabri if there are no problems caused by your previous treatment.

- Your doctor will order **blood tests** for antibodies to the JC virus and other possible problems.
- Your doctor will arrange an **MRI scan**, which will be repeated during treatment.
- **To switch from some MS medicines,** your doctor may advise you to wait for a certain time to ensure that most of the previous medicine has left your body.
- For adults the recommended dose is 300 mg, given once every 4 weeks.
- Tysabri must be diluted before it is given to you. It is given as a drip into a vein (by intravenous infusion), usually in your arm. This takes about 1 hour.
- Information for medical or healthcare professionals on how to prepare and administer the medicine is provided at the end of this leaflet.

If you stop using Tysabri
Regular dosing with Tysabri is important, especially in the first few months of treatment. It is important to continue with your medicine for as long as you and your doctor decide that it is helping you. Patients who received one or two doses of Tysabri, and then had a gap in treatment of three months or more, were more likely to have an allergic reaction when restarting treatment.

Checking for allergic reactions
A few patients have had an allergic reaction to this medicine. Your doctor will check for allergic reactions during the infusion and for 1 hour afterwards. See also section 4, *Possible side effects*.

If you miss your dose of Tysabri
If you miss your usual dose of Tysabri, arrange with your doctor to receive it as soon as you can. You can then continue to receive your dose of Tysabri every 4 weeks.

Will Tysabri always work?
In a few patients receiving Tysabri, the body's natural defences may stop the medicine from working properly over time, as the body develops antibodies to the medicine. Your doctor can decide whether this medicine is not working properly for you from blood tests and will stop the treatment, if necessary.

If you have any further questions on Tysabri, ask your doctor. Always use this medicine exactly as described in this leaflet or as your doctor has told you. Check with your doctor if you are not sure.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Speak to your doctor or nurse immediately if you notice any of the following.

Signs of a brain infection

- Changes in personality and behaviour such as confusion, delirium or loss of consciousness,
- Seizures (fits)
- Headache
- Nausea / vomiting
- Stiff neck
- Extreme sensitivity to bright light
- Fever
- Rash (anywhere on the body)

These symptoms may be caused by an infection of the brain (*encephalitis or PML*) or its covering layer (*meningitis*).

Signs of other serious infections

- An unexplained fever
- Severe diarrhoea
- Shortness of breath
- Prolonged dizziness
- Headache
- Weight loss
- Listlessness
- Impaired vision
- Pain or redness of the eye(s)

Signs of an allergic reaction

- Itchy rash (*hives*)
- Swelling of your face, lips or tongue
- Difficulty breathing
- Chest pain or discomfort
- Increase or decrease in your blood pressure (your doctor or nurse will notice this if they are monitoring your blood pressure)

These are most likely during or shortly after the infusion.

Signs of a possible liver problem
- Yellowing of your skin or the whites of your eyes
- Unusual darkening of the urine
- Abnormal liver function test

Speak to a doctor or nurse immediately if you get any of the side effects listed above, or if you think you have an infection. **Show your patient alert card** and this package leaflet to any doctor or nurse who treats you, not only to your neurologist.

Other side effects
Very common (may affect more than 1 in 10 people)
- Urinary tract infection
- Sore throat and runny or blocked up nose
- Headache
- Dizziness
- Feeling sick (*nausea*)
- Joint pain
- Tiredness
- Dizziness, feeling sick (*nausea*), itching and chills during or shortly after infusion

Common (may affect up to 1 in 10 people)
- Anaemia (decrease in your red blood cells which can make your skin pale and can make you feel breathless or lacking energy)
- Allergy (*hypersensitivity*)
- Shivering
- Itchy rash (*hives*)
- Being sick (*vomiting*)
- Fever
- Difficulty breathing (*dyspnoea)*
- Reddening of the face or body (*flushing*)
- Herpes infections
- Discomfort around the place you have had your infusion. You could experience bruising, redness, pain, itching or swelling

Uncommon (may affect up to 1 in 100 people)
- Severe allergy (*anaphylactic reaction*)
- Progressive multifocal leukoencephalopathy (PML)
- Inflammatory disorder after discontinuation of the medicinal product
- Facial swelling
- An increase in the number of white blood cells (*eosinophilia*)

Rare (may affect up to 1 in 1,000 people)

- Herpes infection in the eye
- Severe anaemia (decrease in your red blood cells which can make your skin pale and can make you feel breathless or lacking energy).
- Severe swelling under the skin
- High levels of bilirubin in the blood (*hyperbilirubinaemia*) which may cause symptoms such as yellowing of your eyes or skin, fever and tiredness

Not known (frequency cannot be estimated from the available data)

- Unusual infections (so-called "*opportunistic infections*")
- Damage to your liver

Speak to your doctor as soon as possible if you think you have an infection.
You will also find this information in the patient alert card you have been given by your doctor.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

Malta
ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

United Kingdom (Northern Ireland)
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tysabri

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label and carton. The expiry date refers to the last day of that month.

Unopened vial:
Store in a refrigerator .
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Diluted solution:
After dilution, immediate use is recommended. If not used immediately, the diluted solution must be stored at 2˚C to 8˚C and infused within 8 hours of dilution.

Do not use this medicine if you notice particles in the liquid and/or the liquid in the vial is discoloured.

6. Contents of the pack and other information

What Tysabri contains
The active substance is natalizumab. Each 15 mL vial of concentrate contains 300 mg natalizumab (20 mg per mL). When diluted, the solution for infusion contains approximately 2.6 mg per mL of natalizumab.

The other ingredients are:
Sodium phosphate, monobasic, monohydrate,
Sodium phosphate, dibasic, heptahydrate,
Sodium chloride (see section 2 'Tysabri contains sodium'),
Polysorbate 80 (E 433)
Water for injections

What Tysabri looks like and contents of the pack
Tysabri is a clear, colourless to slightly cloudy liquid.
Each carton contains one glass vial.

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Manufacturer
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For any further information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in 03/2021

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

1. Inspect the Tysabri vial for particles prior to dilution and administration. If particles are observed and/or the liquid in the vial is not colourless, clear to slightly opalescent, the vial must not be used.

2. Use aseptic technique when preparing the medicine. Remove flip-top from the vial. Insert the syringe needle into the vial through the centre of the rubber stopper and remove 15 mL concentrate for solution for infusion.

3. Add the 15 mL concentrate for solution for infusion to 100 mL sodium chloride 9 mg/mL (0.9%) solution for injection. Gently invert the solution to mix completely. Do not shake.

4. Tysabri must not be mixed with other medicinal products or diluents.

5. Visually inspect the diluted medicinal product for particles or discolouration prior to administration. Do not use if it is discoloured or if foreign particles are seen.

6. The diluted medicinal product is to be used as soon as possible and within 8 hours of dilution. If the diluted medicinal product is stored at 2 to 8°C (do not freeze), allow the solution to warm to room temperature prior to infusion.

7. The diluted solution is to be infused intravenously over 1 hour at a rate of approximately 2 mL per minute.

8. After the infusion is complete, flush the intravenous line with sodium chloride 9 mg/mL (0.9%) solution for injection.

9. Each vial is for single–use only.

10. In order to improve traceability of biological medicinal products, the product name (Tysabri) and batch number of the administered product should be clearly recorded.

11. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the patient

Tysabri 150 mg solution for injection in pre-filled syringe
natalizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

In addition to this leaflet you will be given a patient alert card. This contains important safety information that you need to know before and during treatment with Tysabri .

- Keep this leaflet and the patient alert card. You may need to read them again. Keep the leaflet and patient alert card with you during treatment and for six months after the last dose of this medicine, as side effects may occur even after you have stopped treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Tysabri is and what it is used for

Tysabri is used to treat multiple sclerosis (MS). It contains the active substance natalizumab. This is called a *monoclonal antibody*.

MS causes inflammation in the brain that damages the nerve cells. This inflammation happens when white blood cells get into the brain and spinal cord. This medicine stops the white blood cells getting through to the brain. This reduces nerve damage caused by MS.

Symptoms of multiple sclerosis
The symptoms of MS vary from patient to patient, and you may experience some or none of them.
They may include: walking problems; numbness in the face, arms or legs; problems with vision; tiredness; feeling off-balance or light headed; bladder and bowel problems; difficulty in thinking and concentrating; depression; acute or chronic pain; sexual problems; stiffness and muscle spasms.

When the symptoms flare up, it is called a *relapse* (also known as an exacerbation or an attack). When a relapse occurs, you may notice the symptoms suddenly, within a few hours, or slowly progressing over several days. Your symptoms will then usually improve gradually (this is called a *remission*).

How Tysabri can help
In trials**,** this medicine approximately halved the build-up of disability caused by MS, and decreased the number of MS attacks by about two-thirds. While you are treated with this medicine you might not notice any improvement, but it may still be working to prevent your MS becoming worse.

2. What you need to know before you receive Tysabri

Before you start treatment with this medicine, it is important that you and your doctor have discussed the benefits you could expect to receive from this treatment and the risks that are associated with it.

You must not be given Tysabri
- If you are **allergic** to natalizumab or any of the other ingredients of this medicine (listed in section 6).

- If you have been **diagnosed with PML** (*progressive multifocal leukoencephalopathy*). PML is an uncommon infection of the brain.

- If your **immune system** has a serious problem. This may be due to disease (such as HIV), or to a medicine you are taking, or have taken in the past (see below).

- If you are taking **medicines that affect your immune system**, including certain other medicines used to treat MS. These medicines cannot be used with Tysabri.

- If you **have cancer** (unless it is a type of skin cancer called *basal cell carcinoma*).

Warnings and precautions
You need to discuss with your doctor whether Tysabri is the most suitable treatment for you. Do this before you start taking this medicine, and when you have been receiving it for more than two years.

Possible brain infection (PML)

Some people receiving this medicine (fewer than 1 in 100) have had an uncommon brain infection called PML (*progressive multifocal leukoencephalopathy*). PML can lead to severe disability or death.

- Before starting treatment, **all patients will have blood tests** arranged by the doctor for JC virus infection. JC virus is a common virus that does not normally make you ill. However, PML is linked to an increase of JC virus in the brain. The reason for this increase in some patients treated with Tysabri is not clear. Before and during treatment, your doctor will test your blood to check if you have antibodies to the JC virus, which are a sign that you have been infected by the JC virus.

- Your doctor will arrange a **Magnetic Resonance Imaging (MRI) scan**, which will be repeated during treatment to rule out PML.

- **The symptoms of PML** may be similar to an MS relapse (see section 4, *Possible side effects*). You can also get PML up to 6 months after stopping Tysabri treatment.

  Tell your doctor as soon as possible if you notice your MS getting worse or if you notice any new symptoms, while you are on Tysabri treatment or for up to 6 months afterwards.

- **Tell your partner or caregivers** about what to look out for (see also section 4, *Possible side effects*). Some symptoms might be difficult to spot by yourself, such as changes in mood or behaviour, confusion, speech and communication difficulties. If you get any of these, **you may need further tests**. Keep looking out for symptoms in the 6 months after stopping Tysabri.

- Keep the patient alert card you have been given by your doctor. It includes this information. Show it to your partner or caregivers.

Three things can increase your risk of PML with Tysabri. If you have two or more of these risk factors, the risk is increased further:

- **If you have antibodies to the JC virus** in your blood. These are a sign that the virus is in your body. You will be tested before and during Tysabri treatment.

- **If you are treated for a long time** with Tysabri, especially if it is more than two years.

- **If you have taken a medicine called an *immunosuppressant***, that reduces the activity of your immune system.

Another condition, called JCV GCN (*JC virus granule cell neuronopathy*), is also caused by JC virus and has occurred in some patients receiving this medicine. The symptoms of JCV GCN are similar to PML.

For those with a lower risk of PML, your doctor may repeat the test regularly to check that:

- You still do not have antibodies to the JC virus in your blood.

- If you have been treated for more than 2 years, you still have a lower level of JC virus antibodies in your blood.

If someone gets PML
PML can be treated, and Tysabri treatment will be stopped. However, some people **get a reaction** as Tysabri is removed from the body. This reaction (known as **IRIS**, or *immune reconstitution inflammatory syndrome*) may lead to your condition getting worse, including worsening of brain function.

Look out for other infections
Some infections other than PML may also be serious and can be due to viruses, bacteria, and other causes.

Tell a doctor or nurse immediately if you think you have an infection (see also section 4, *Possible side effects*).

Children and adolescents
Do not give this medicine to children or adolescents under the age of 18 years.
.
Other medicines and Tysabri
Tell your doctor if you are taking, have recently taken or might take any other medicines.

- **You must not be given this medicine** if you are now being treated with medicines that affect your **immune system**, including certain other medicines to treat your MS.

- You might not be able to use this medicine if you have **previously** had any medicines that affect your immune system.

Pregnancy and breast-feeding
- **Do not use this medicine if you are pregnant**, unless you have discussed this with your doctor. Be sure to tell your doctor immediately if you get pregnant, think you may be pregnant, or if you are planning to become pregnant.

- **Do not breast-feed whilst using Tysabri**. Your doctor will help you decide whether you should stop breast-feeding, or stop using the medicine.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. The risk to the baby and benefit to the mother will be taken into consideration by your doctor.

Driving and using machines
Dizziness is a very common side effect. If you are affected, do not drive or use machines.

Tysabri contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 300 mg dose, so it is essentially 'sodium-free'.

3. How Tysabri is given

Tysabri injections will be given to you, by a doctor experienced in the treatment of MS. Your doctor may switch you directly from another medicine to Tysabri if there are no signs of problems caused by your previous treatment.

- Your doctor will order **blood tests** for antibodies to the JC virus and other possible problems.

- Your doctor will arrange an **MRI scan**, which will be repeated during treatment.
- **To switch from some MS medicines,** your doctor may advise you to wait for a certain time to ensure that most of the previous medicine has left your body.
- For adults the recommended dose is 300 mg, given once every 4 weeks.
- Each dose is given as **two injections** under the skin, in your thigh, stomach or back of your arm. This takes up to 30 minutes.
- Information for medical or healthcare professionals on how to prepare and inject the medicine is provided at the end of this leaflet.

If you stop using Tysabri
Regular dosing with this medicine is important, especially in the first few months of treatment. It is important to continue with your medicine for as long as you and your doctor decide that it is helping you. Patients who received one or two doses of Tysabri, and then had a gap in treatment of three months or more, were more likely to have an allergic reaction when restarting treatment.

Checking for allergic reactions
A few patients have had an allergic reaction to this medicine. Your doctor may check for allergic reactions during the injections and for 1 hour afterwards. See also section 4, *Possible side effects*.

If you miss your dose of Tysabri
If you miss your usual dose of Tysabri, arrange with your doctor to receive it as soon as you can. You can then continue to receive your dose of Tysabri every 4 weeks.

Will Tysabri always work?
In a few patients receiving Tysabri, the body's natural defences may stop the medicine from working properly over time, as the body develops antibodies to the medicine. Your doctor can decide whether this medicine is not working properly for you from blood tests and will stop the treatment, if necessary.

If you have any further questions on Tysabri, ask your doctor. Always use this medicine exactly as described in this leaflet or as your doctor has told you. Check with your doctor if you are not sure.

Subcutaneous is abbreviated as SC on the syringe label.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Speak to your doctor or nurse immediately if you notice any of the following.

Signs of a brain infection

- Changes in personality and behaviour such as confusion, delirium or loss of consciousness,
- Seizures (fits)
- Headache
- Nausea / vomiting
- Stiff neck
- Extreme sensitivity to bright light
- Fever
- Rash (anywhere on the body)

These symptoms may be caused by an infection of the brain (*encephalitis or PML*) or its covering layer (*meningitis*).

Signs of other serious infections

- An unexplained fever
- Severe diarrhoea
- Shortness of breath
- Prolonged dizziness
- Headache
- Weight loss
- Listlessness
- Impaired vision
- Pain or redness of the eye(s)

Signs of an allergic reaction

- Itchy rash (*hives*)
- Swelling of your face, lips or tongue
- Difficulty breathing
- Chest pain or discomfort
- Increase or decrease in your blood pressure (your doctor or nurse will notice this if they are monitoring your blood pressure)

These are most likely during or shortly after the injection.

Signs of a possible liver problem

- Yellowing of your skin or the whites of your eyes
- Unusual darkening of the urine
- Abnormal liver function test

Speak to a doctor or nurse immediately if you get any of the side effects listed above, or if you think you have an infection. **Show your patient alert card** and this package leaflet to any doctor or nurse who treats you, not only to your neurologist.

Other side effects

Very common (may affect more than 1 in 10 people)

- Urinary tract infection
- Sore throat and runny or blocked up nose
- Headache
- Dizziness
- Feeling sick (*nausea*)
- Joint pain
- Tiredness

Common (may affect up to 1 in 10 people)

- Anaemia (decrease in your red blood cells which can make your skin pale and can make you feel breathless or lacking energy)
- Allergy (*hypersensitivity*)
- Shivering
- Itchy rash (*hives*)
- Being sick (*vomiting*)
- Fever
- Difficulty breathing (*dyspnoea*)
- Reddening of the face or body (*flushing*)
- Herpes infections
- Discomfort around the place you have been injected. You could experience pain, bruising, redness, itching or swelling

Uncommon (may affect up to 1 in 100 people)

- Severe allergy (*anaphylactic reaction*)
- Progressive multifocal leukoencephalopathy (PML)
- Inflammatory disorder after discontinuation of the medicinal product
- Facial swelling
- An increase in the number of white blood cells (*eosinophilia*)

Rare (may affect up to 1 in 1,000 people)

- Herpes infection in the eye
- Severe anaemia (decrease in your red blood cells which can make your skin pale and can make you feel breathless or lacking energy)
- Severe swelling under the skin
- High levels of bilirubin in the blood (*hyperbilirubinaemia)* which may cause symptoms such as yellowing of your ees or skin, fever and tiredness

Not known (frequency cannot be estimated from the available data**)**

- Unusual infections of brain and eyes
- Damage to your liver

Speak to your doctor as soon as possible if you think you have an infection.You will also find this information in the patient alert card you have been given by your doctor.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

Malta
ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

United Kingdom (Northern Ireland)
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tysabri

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label and carton. The expiry date refers to the last day of that month.

Store in a refrigerator.
Do not freeze.
The syringes can be kept in their original packaging for up to 24 hours at room temperature (up to 25° C). The syringes must not be returned to the refrigerator.
Keep the syringes in the outer carton in order to protect from light.

Do not use this medicine if you notice particles in the liquid and/or the liquid in the syringe is discoloured.

6. Contents of the pack and other information

What Tysabri contains
The active substance is natalizumab.
Each 1 mL pre-filled syringe contains 150 mg natalizumab.

The other ingredients are:
Sodium phosphate, monobasic, monohydrate,
Sodium phosphate, dibasic, heptahydrate,
Sodium chloride (see section 2 ‘Tysabri contains sodium’),
Polysorbate 80 (E 433)
Water for injections

What Tysabri looks like and contents of the pack
Tysabri is a colourless to slightly yellow, slightly opalescent to opalescent liquid.

Each carton contains two syringes.
Tysabri is available in packs containing 2 pre-filled syringes.

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For any further information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in 03/2021

Other sources of information

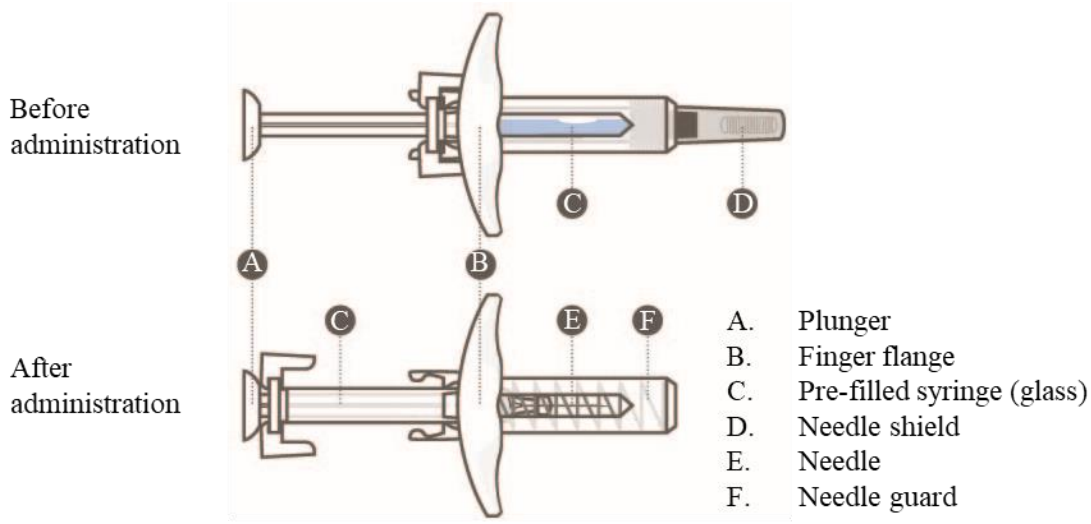
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

The 300 mg recommended dose should be administered using two 150 mg pre-filled syringes, see section 3 below.

Instructions for administration

The pre-filled syringe has a needle guard system that will automatically activate when the plunger is fully depressed. As you let go of the plunger, the needle guard will cover the exposed needle.



1. Remove dose pack from the refrigerator and allow to warm to room temperature (up to 25°C) before administering the injections. Recommended warm up time is 30 minutes.

Date and time of removal of the dose pack from the refrigerator must be recorded on the carton.

- **Do not use external heat sources** such as hot water to warm the pre-filled syringes.
- **Do not** touch or recap the needle at any stage. This is to avoid accidental needle stick injury.

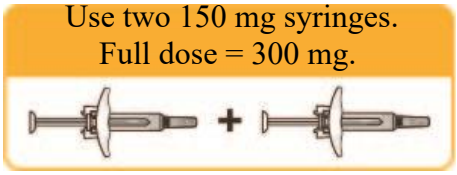
2. **Remove both product syringes** from the tray. Check that the medicinal product in each pre-filled syringe is a colourless to slightly yellow, slightly opalescent solution that is essentially free of visible particles. You might see air bubbles in the display windows. This is normal and will not affect the dose.

- **Check both** the pre-filled syringes. **Do not** use them if:
  - they are past the expiry date marked on the syringe label (EXP).

  or
  - have been stored at room temperature (up to 25°C) for longer than 24 hours.
  - the colour and clarity of the liquid is not consistent with the above, or if the liquid contains floating particles.
  - there are any signs of damage (cracks, chips, etc.).

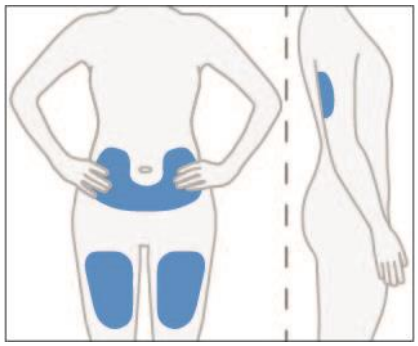
- If you notice any of the above, contact your pharmacy **immediately**.

3. A full dose is equivalent to two syringes administered consecutively and within 30 minutes of each other.



4. Use aseptic technique (clean and germ free) and a flat work surface during the injection procedure.

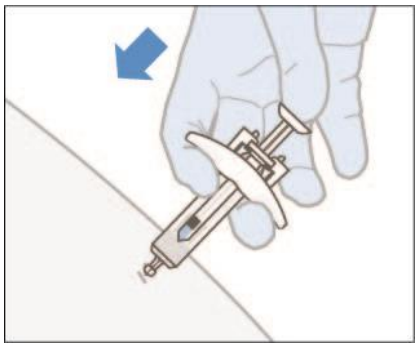
5. Choose the first subcutaneous injection site in the thigh, abdomen, or the back of the upper arm.



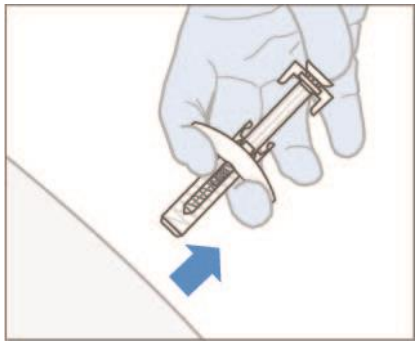
- **Do not** inject into an area of the body where the skin is irritated, reddened, bruised, infected, or scarred in any way.

6. Give the first injection.
    - Choose an injection site and wipe the skin with an alcohol wipe.
    - Let the injection site dry on its own before injecting.
    - **Do not** touch or blow on this area again before giving the injection.
    - Remove the needle shield.
    - Gently pinch the skin around the cleaned injection site using thumb and forefinger to create a slight bulge.
    - Hold the pre-filled syringe at a 45°-90° angle to the injection site. Quickly insert the needle straight into the skin fold until the needle is fully under the skin.

7. Slowly push the plunger in one smooth motion until the syringe is completely empty. Do not pull back on the plunger.



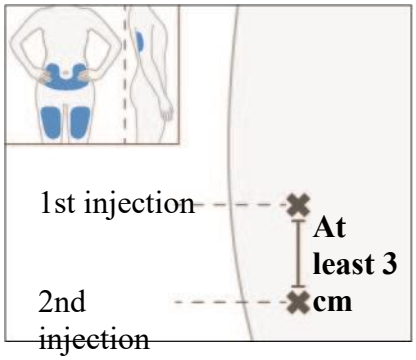
8. Before removing the syringe, check that the syringe is empty. If you see any blood, press a cotton ball or gauze on the site. Do not rub the skin after the injection.When removing the syringe from the injection site, let go of the plunger WHILE pulling the needle straight out. As you let go of the plunger, the needle guard will cover the exposed needle.



9. Administer injections one after the other without significant delay. In the event that the second injection cannot be administered immediately following the first injection, the second injection should be administered no later than 30 minutes after the first injection. The second injection should be at least 3 cm away from the first injection location.

Patients should be **observed during the subcutaneous injections and for 1 hour after** for signs and symptoms of injection reactions including hypersensitivity. **After the first 6 Tysabri doses**, regardless of route of administration, patients should be observed after subcutaneous injection according to clinical judgement.

Promptly discontinue injection upon the first observation of any signs or symptoms consistent with an allergic reaction [see SmPC section 4.4].



10. Dispose of the used syringe in accordance with local requirements.

APPENDIX 3. PATIENT ALERT CARD

TYSABRI Patient Alert Card

Patient's Name:
_____
Doctor's Name:
_____
Doctor's Phone:
_____
Date TYSABRI Started:
_____

This alert card contains important safety information that you need to be aware of before, during and after stopping treatment with TYSABRI.

- Show this card to any doctor involved with your treatment, not only to your neurologist.
- Please read the TYSABRI 'Package Leaflet' carefully before you start using this medicine.
- Keep this card with you during Tysabri treatment and 6 months after the last dose of TYSABRI, since side effects may occur even after you have stopped treatment with TYSABRI.
- Show this card to your partner or caregivers. They might see symptoms of PML that you might not notice, such as changes in mood or behaviour, memory lapses, speech and communication difficulties. You should remain aware of symptoms that might arise for up to 6 months after stopping TYSABRI treatment.

Prior to treatment with TYSABRI

- You should not be treated with TYSABRI if you have a serious problem with your immune system

During treatment with TYSABRI

Progressive Multifocal Leukoencephalopathy (PML)
PML, a rare brain infection, has occurred in patients who have been given TYSABRI. PML usually leads to severe disability or death.

The risk of PML appears to increase with treatment duration, especially beyond 2 years.

The symptoms of PML may be similar to an MS relapse. Therefore, if you believe your MS is getting worse or if you notice any new symptoms while you are on TYSABRI treatment or for up to 6 months after stopping TYSABRI treatment, it is very important that you speak to your doctor as soon as possible. PML symptoms generally develop more slowly than those associated with an MS relapse (over days or weeks), and may be similar to your MS symptoms.

Signs include:
- Changes in mental ability and concentration,
- Behavioural changes,
- Weakness on one side of the body,
- Vision problems,
- New neurological symptoms that are unusual for you.

Management of PML requires immediately stopping TYSABRI treatment.

Serious Infections
Other serious infections may occur with TYSABRI. Speak to your doctor as soon as possible if you think you have developed a severe, persistent infection, for example a persistent fever.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes

• You should not take any other long-term medicines for your multiple sclerosis while receiving TYSABRI	any possible side effects not listed in the package leaflet. You can also report side effects directly via the national reporting system: The Malta Medicines Authority should be informed about any cases of PML. Report forms can be downloaded from http://www.medicines authority.gov.mt/adrportal and sent by post or email to: Post: ADR Reporting Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann SGN 3000, Malta Email: postlicensing.medicinesauthority@gov.mt By reporting side affects you can help provide more information on the safety of this medicine. **25/03/2021**

APPENDIX 4. TREATMENT INITIATION FORM, TREATMENT CONTINUATION FORM, AND TREATMENT DISCONTINUATION FORM

TYSABRI Treatment Initiation Form

This form should be read carefully before starting treatment with TYSABRI. Please follow the advice in this form to ensure that you are fully informed of, and understand the risk of PML (progressive multifocal leukoencephalopathy), IRIS (Immune reconstitution Inflammatory Syndrome) and other important adverse effects of TYSABRI.

Before starting treatment with TYSABRI you should:

- **Read the Package Leaflet which is included in each box of TYSABRI**
- **Read the Alert Card given to you by your doctor**
- **Discuss with your doctor the benefits and the risks associated with this treatment**

The Package Leaflet and the Alert Card contain important safety information about PML, a rare brain infection that has occurred in patients who have been given TYSABRI, and which may lead to severe disability or death.

JC virus is a common virus which infects many people but does not normally cause noticeable illness. PML is associated with an uncontrolled increase of the JC virus in the brain, although the reason for this increase in some patients treated with TYSABRI is unknown.

The risk of PML with TYSABRI is higher:

- If you have antibodies to the JC virus in your blood
- The longer that you are on treatment with TYSABRI, especially if you have been on treatment for more than two years
- If you have taken an immunosuppressant (a medicine that reduces the activity of your body's immune system) at any time before starting TYSABRI treatment.

Your doctor should discuss the potential risk of developing PML with you before you start treatment with TYSABRI.

Your doctor may test your blood to check if you have antibodies to the JC virus before you start treatment with TYSABRI. Your doctor may repeat the test while you are on TYSABRI treatment to check if anything has changed. The risk of PML is higher if you have all the risk factors described above, or if you have not taken an immunosuppressant medication prior to starting TYSABRI and have higher levels of antibodies to the JC virus and you have been on TYSABRI for more than 2 years. Your doctor will monitor you more closely if you are at higher risk for PML.

You should discuss with your doctor if TYSABRI is the most suitable treatment for you before you start taking TYSABRI and when you have been taking TYSABRI for more than two years.

In patients with PML, a reaction known as IRIS (Immune Reconstitution Inflammatory Syndrome) is likely to occur after treatment for PML, as TYSABRI is removed from your body. IRIS may lead to your condition getting worse, including worsening of brain function.

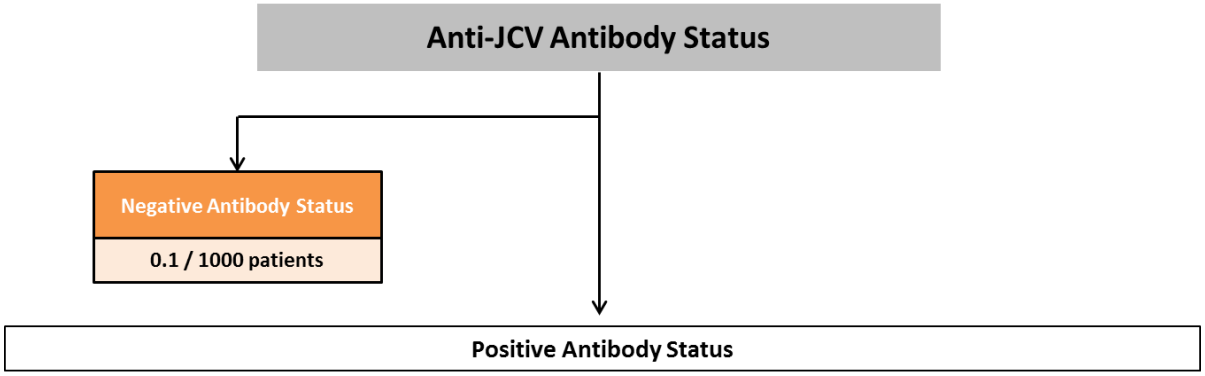
The Package Leaflet should be read each time that you take TYSABRI because it may have new information that is important to your treatment.

You should keep the Alert Card with you to remind you of the important safety information, in particular any symptoms you may develop which could possibly indicate PML. If appropriate, you should show the Alert Card to your partner or caregiver.

If you do not have the Package Leaflet or the Alert Card, then please ask your doctor to provide them to you before you initiate your TYSABRI treatment.

[*Patient's name, signature and date of signature, and Doctor's name, signature, and date of signature*].

PML risk estimate:



Natalizumab Exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with prior IS use
	No index value	Antibody Index ≤ 0.9	Antibody Index > 0.9 ≤ 1.5	Antibody Index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
37-48 months	4	0.4	2	7	8
49-60 months	5	0.5	2	8	8
61-72 months	6	0.6	3	10	6

Patients who are anti-JCV antibody negative

Based on global data, if you do not have antibodies to JCV your chance of getting PML is 0.1/1000 (or 1 in 10,000) patients.

Patients who are anti-JCV antibody positive

If you do have antibodies to JCV, your risk of developing PML will vary depending on the duration of treatment with TYSABRI, the level of anti-JCV antibodies in your blood and whether you have received prior treatment with an immunosuppressant medication. Your doctor will discuss the potential risk before you start treatment.

Reporting of side effects

The Malta Medicines Authority should be informed about any cases of PML. Report forms can be downloaded from http://www.medicines authority.gov.mt/adrportal and sent by post or email to:
Post: ADR Reporting
Sir Temi Zammit Buildings,
Malta Life Sciences Park,
San Gwann
SGN 3000,
Malta

Email: postlicensing.medicinesauthority@gov.mt

As TYSABRI is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.

25/03/2021

TYSABRI Treatment Continuation Form

This form should be read carefully before continuing TYSABRI treatment for more than 2 years. Although you have been receiving TYSABRI for 2 years, it is important that you are reminded that the risk of PML increases beyond this time. Please follow the advice in this form to ensure that you are fully informed of, and understand the risk of PML (progressive multifocal leukoencephalopathy), IRIS (Immune reconstitution Inflammatory Syndrome) and other important adverse effects of TYSABRI.

Before continuing treatment with TYSABRI you should:

- **Read the Package Leaflet which is included in each box of TYSABRI**
- **Read the Alert Card given to you by your doctor**
- **Discuss with your doctor the benefits and the risks associated this treatment**

The Package Leaflet and the Alert Card contain important safety information about PML, a rare brain infection that has occurred in patients who have been given TYSABRI, and which may lead to severe disability or death.

PML is associated with an uncontrolled increase of the JC virus in the brain, although the reason for this increase in some patients treated with TYSABRI is unknown. JC virus is a common virus which infects many people but does not normally cause noticeable illness.

The risk of PML with TYSABRI is higher:

- **If you have antibodies to the JC virus in your blood.**
- **The longer that you are on treatment with TYSABRI, especially if you have been on treatment for more than two years.**
- **If you have taken an immunosuppressant (a medicine that reduces the activity of your body's immune system) at any time before starting TYSABRI treatment.**

Your doctor should discuss the potential risk of developing PML with you before you continue treatment with TYSABRI.

Your doctor may test your blood to check if you have antibodies to the JC virus before you continue treatment with TYSABRI. Your doctor may repeat the test while you are on TYSABRI treatment to check if anything has changed. The risk of PML is higher if you have all the risk factors described above, or if you have not taken an immunosuppressant medication prior to starting TYSABRI and have higher levels of antibodies to the JC virus and you have been on TYSABRI for more than 2 years. Your doctor will monitor you more closely if you are at higher risk for PML.

You should discuss with your doctor if TYSABRI is the most suitable treatment for you before you continue TYSABRI for more than two years.

In patients with PML, a reaction known as IRIS (Immune Reconstitution Inflammatory Syndrome) is likely to occur after treatment for PML, as TYSABRI is removed from your body. IRIS may lead to your condition getting worse, including worsening of brain function.

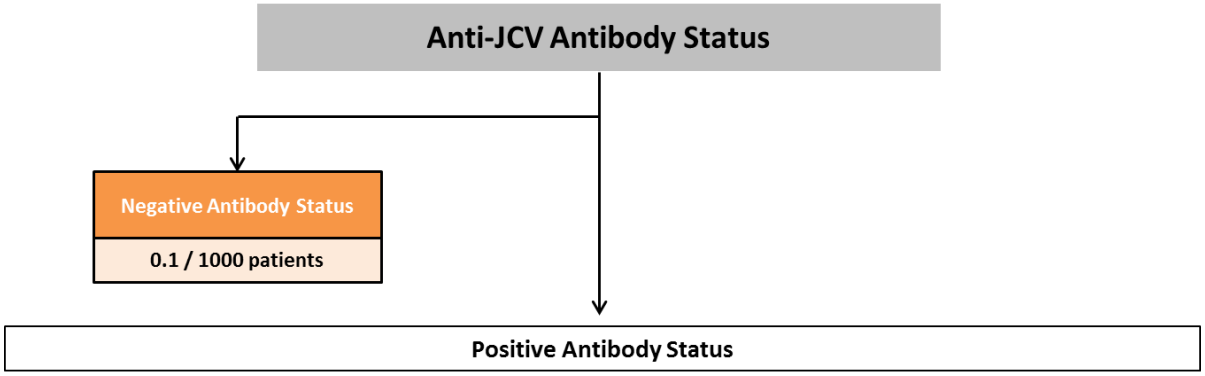
The Package Leaflet should be read each time that you take TYSABRI because it may have new information that is important to your treatment.

You should keep the Alert Card with you to remind you of the important safety information, in particular any symptoms you may develop which could possibly indicate PML. If appropriate, you should show the Alert Card to your partner or caregiver.

If you do not have the Package Leaflet or the Alert Card, then please ask your doctor to provide them to you before you receive your TYSABRI treatment.

[*Patient's name, signature and date of signature, and Doctor's name, signature, and date of signature*].

PML risk estimate:



Natalizumab Exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with prior IS use
	No index value	Antibody Index ≤ 0.9	Antibody Index > 0.9 ≤ 1.5	Antibody Index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
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61-72 months	6	0.6	3	10	6

Patients who are anti-JCV antibody negative

Based on global data, if you do not have antibodies to JCV your chance of getting PML is 0.1/1000 (or 1 in 10,000) patients.

Patients who are anti-JCV antibody positive

If you do have antibodies to JCV, your risk of developing PML will vary depending on the duration of treatment with TYSABRI, the level of anti-JCV antibodies in your blood and whether you have received prior treatment with an immunosuppressant medication. Your doctor will discuss the potential risk before you continue with treatment.

Reporting of side effects

National explanatory text to be inserted. As TYSABRI is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.

25/03/2021

TYSABRI Treatment Discontinuation Form

This form should be read carefully before discontinuing treatment with TYSABRI. Please follow the advice in this form to ensure that you are fully informed of, and understand the continued risk of PML (progressive multifocal leukoencephalopathy) for up to 6 months following discontinuation of TYSABRI.

Before starting treatment with TYSABRI you should have received an Alert Card from your doctor. This Alert Card should be kept for 6 months after discontinuation of treatment as it has important information about PML for your reference.

PML is a rare brain infection that has occurred in patients who have been given TYSABRI, and which may lead to severe disability or death. PML has been reported up to 6 months after discontinuation of TYSABRI.
Signs include:
- changes in mental ability and concentration,
- behavioural changes,
- weakness on one side of the body,
- vision problems,
- new neurological symptoms that are unusual for you.

Symptoms of PML may be similar to an MS relapse. Therefore, if you believe your MS is getting worse or if you notice any new symptoms for up to 6 months after stopping TYSABRI treatment, it is very important that you speak to your doctor as soon as possible

During the 6 months following treatment discontinuation of TYSABRI, your doctor will monitor you and will decide when you should receive MRI imaging. In general, you will continue to receive 3-6 month MRI imaging if you have either of the following combination of PML risk factors:

- You have antibodies to the JC virus, have taken TYSABRI for more than 2 years and previously taken an immunosuppressant (a medicine that reduces the activity of your body's immune system) at any time before starting TYSABRI.
- You have never taken an immunosuppressant therapy before starting TYSABRI, but have taken TYSABRI for more than 2 years and have a high anti-JCV antibody index (increased amount of antibody in your blood).

If you do not fall into one of the above groups, then you will continue to receive routine MRIs as prescribed by your doctor.

Should you have any questions about the above information, please ask your doctor.

If you do not have the Alert Card that you received when starting TYSABRI, then please ask your doctor for a new card. You should keep the Alert Card with you to remind you of the important safety information, in particular any symptoms you may develop which could possibly indicate PML, if appropriate, you should show the Alert Card to your partner or caregiver.

[*Patient's name, signature and date of signature, and Doctor's name, signature and date of signature*].

Reporting of side effects

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to;
P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000
E: postlicensing.medicinesauthority@gov.mt

Or to the local agent on behalf of the MAH:

All reports can be sent to pharmacovigilance@pharmamt.com or by post to:

103, Stuart Street,

Gzira, GZR 1054

As TYSABRI is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.

25/03/2021