Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

NATALIZUMAB PROTOCOL FOR THE TREATMENT OF RELAPSING REMITTING MULTIPLE SCLEROSIS (RRMS)

Natalizumab Therapy

INDICATIONS FOR USE:

TREATMENT	INDICATION	ICD10	Protocol Code
Natalizumab (Tysabri®)	Natalizumab (Tysabri®) is indicated as single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis 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* **ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS** *section below and the Summary of Product Characteristics*)	**G35**	**MS101a**
	OR		
	Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.	**G35**	**MS101b**

NOTE: all prescribers must ensure they are familiar with the *Physician Information and Management Guidelines.* See ***SUPPORT RESOURCES*** section below.

ELIGIBILTY:

- Indications as above
- Patient aged 18-65 (not recommended for use in patients aged over 65 due to a lack of data in this population; safety and efficacy not established in children and adolescents up to 18years)

EXCLUSIONS/CONTRAINDICATIONS:

- Hypersensitivity to natalizumab or to any of the excipients in the formulation.
- 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)
- Combination with other disease modifying therapies. Due to a lack of safety data, natalizumab is not recommended in patients previously administered alemtuzumab or cladribine unless potential benefits clearly outweigh risks for an individual patient.
- Known active malignancies, except for patients with cutaneous basal cell carcinoma

USE with CAUTION:

- In patients who have been exposed to prior immunosuppressive medicinal products with potential to cause prolonged immunosuppression after discontinuation (e.g. azathioprine, methotrexate, cyclophosphamide, mitoxantrone etc.). The physician must confirm that such patients are not immunocompromised before starting treatment with natalizumab.
- In pregnancy and lactation
- In patients on a modified sodium diet
- Abnormal liver function

TESTS:

Baseline Measures:

- MRI scan within 3 months prior to treatment

Baseline tests:

- FBC, U&E, LFTs.
- Record prior immunosuppression use
- John Cunningham virus (JCV) antibody Index Status
- Varicella Zoster Virus (VZV) Serology - VZV vaccination of antibody-negative patients should be considered at least 6 weeks in advance of treatment

NOTE: *use of plasmapheresis (PLEX) or intravenous immunoglobulin (IVIg) can affect meaningful interpretation of anti-JCV antibody testing. Patients should not be tested for anti-JCV antibodies within two weeks of PLEX (due to removal of antibodies from the serum) or six months of IVIg (5x half-life of IVIg).*

Regular tests:

- FBC, U&E and LFTs every 3 months
- anti-JCV antibody every 6 months
- MRI scanning:
  - All patients should have a repeat MRI 6 months after starting treatment to be used as the baseline scan for future comparisons of efficacy
  - JCV antibody negative – repeat MRI annually
  - JCV antibody positive (index <1.5) – after 18months treatment repeat MRI 6 monthly
  - JCV antibody positive (index >1.5) – repeat MRI 4 monthly (modified protocol could be used for safety scans)

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

TREATMENT:

Treatment 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.

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).

Natalizumab protocol for use by clinical staff treating patients with relapsing remitting multiple sclerosis (RRMS) in acute hospitals.

Drug	Dose	Route	Diluent & Rate	Cycle
Natalizumab	300mg	Intravenous infusion	100ml 0.9% Sodium Chloride over 1 hour at a rate of approximately 2 ml/minute.	Every 28 days
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. Resources for the management of hypersensitivity reactions should be available.				

Drug	Dose	Route	Method of Administration	Cycle
Natalizumab	300mg (2 X 150mg pre-filled syringe)	Subcutaneous	One after the other, the second injection should be administered not later than 30 minutes after the first.	Every 28 days
The second injection should be more than 3 cm away from the first injection location. Patients are to be observed during the subcutaneous injections and for 1 hour after the completion for signs and symptoms of hypersensitivity reactions. Resources for the management of hypersensitivity reactions should be available. After first 6 doses, if the patient according to clinical judgement has not experienced any injection reactions, the observation time can be reduced or removed.				

Any switch in route of administration of the medicinal product should be made 4 weeks after the previous dose.
Treatment with natalizumab is administered once every 28 days for up to 2 years. After 2 years, re-affirm disease status and ensure benefit of treatment outweighs risk of PML (as determined by Neurologist in collaboration with patient).

Risk factors for developing PML during natalizumab therapy include:

- Duration of natalizumab treatment; especially beyond 2 years
- Immunosuppressant use prior to receiving natalizumab
- Presence of anti-JCV antibodies

It is postulated that extending the dosing interval may reduce the risk of the development of PML – see **DOSE MODIFICATIONS** section below for further information.

Patients treated with natalizumab must be given the patient alert card and be informed about the risks of the medicinal product (see also package leaflet).

After two years of treatment, patients should be re-informed about the risks of natalizumab, especially the increased risk of Progressive Multifocal Leukoencephalopathy (PML), and should be instructed together with their caregivers on early signs and symptoms of PML.

DOSE MODIFICATIONS:

Extended Interval Dosing: If natalizumab is considered by the clinical team to be the best therapeutic option available for a patient with an elevated risk of developing PML, extended interval dosing may be considered with the appropriate monitoring.

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 (**NOTE:** this is an unlicensed frequency of administration). For further information, refer to the Summary of Product Characteristics and the *Physician Information and Management Guidelines.*

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 extended interval dosing with the subcutaneous route of administration.

Natalizumab should be **discontinued** if one or more of the following criteria are met:

1. Unacceptable adverse effects of natalizumab, including anaphylactic reaction.
2. Development of confirmed Progressive Multifocal Leukoencephalopathy (PML).
3. No reduction in frequency or severity of relapses compared with pre-treatment phase following a minimum 6 month period of natalizumab treatment *(treatment failure – alternative should be considered)*
4. Radiological evidence of on-going disease activity after at least twelve months of natalizumab treatment i.e. greater than or equal to 2 new lesions, however every new lesion should be assessed for the possibility of PML. The patient is pregnant, breast feeding or attempting conception (Treatment suspended and restarted in the post-partum period when deemed appropriate by the treating neurologist with patient agreement).
5. Development of clinically confirmed secondary progressive MS causing inability to walk, even with aid, for more than 6 months

See **ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS** section below and Summary of Product Characteristics for further information on discontinuation of treatment.

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.

SUPPORTIVE CARE:

PREMEDICATIONS: None

TAKE HOME MEDICATIONS: None

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

Progressive Multifocal Leukoencephalopathy (PML): Use of natalizumab has been associated with an increased risk of PML, an opportunistic infection caused by the JC virus which may be fatal or result in severe disability. Due to this increased risk of developing PML, the benefits and risks of natalizumab treatment should be individually considered 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. If patients develop PML, natalizumab should be permanently discontinued. Immune Reconstitution Inflammatory Syndrome (IRIS) occurs in almost all PML patients after withdrawal or removal (e.g. PLEX) of natalizumab. IRIS can lead to serious neurological complications and can be fatal, see *Physician Information and Management Guidelines* for further information.

In patients considered at high risk of PML, treatment with natalizumab 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 (see Support Resources for link below). PML has been reported following discontinuation of natalizumab 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.

Other Opportunistic Infections: Natalizumab increases the risk of developing encephalitis and meningitis caused by *Herpes Simplex* and *Varicella Zoster* virsuses. Serious, life-threatening and sometimes fatal cases have been reported; if herpes encephalitis or meningitis occurs the medicinal product should be discontinued and appropriate treatment administered.

Loss of vision as a result of acute retinal necrosis (ARN) caused by the herpes virus has been reported. Patients presenting with eye symptoms such as loss of visual acuity, redness, and painful eye should be referred for retinal screening. Discontinuation of natalizumab should be considered following clinical diagnosis of ARN.

Other opportunistic infections may occur during natalizumab therapy. If an opportunistic infection is suspected dosing with natalizumab should be suspended until such infections can be excluded through further investigations. If an opportunistic infection is confirmed dosing must be permanently discontinued.

Hypersensitivity: Hypersensitivity reactions have been associated with natalizumab including serious systemic reactions. 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 natalizumab 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.

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 natalizumab and an increased incidence of

hypersensitivity reactions. Since patients who have received an initial short exposure to natalizumab and then had an extended period without treatment are at a higher risk of developing anti-natalizumab antibodies and/or hypersensitivity upon re-dosing, 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.

Hepatic Events: Spontaneous cases of serious liver injuries, increased liver enzymes, and hyperbilirubinaemia have been reported during the post marketing phase. These liver injuries may occur at any time during treatment. Patients should be monitored at regular intervals for impaired liver function and be instructed to contact their physician if they develop signs or symptoms suggestive of liver injury occur (e.g. jaundice and vomiting). Natalizumab treatment should be discontinued in patients with significant liver injury.

Discontinuation of Natalizumab therapy: There is a significant risk of disease reactivation following cessation of natalizumab therapy; including "rebound activity" where the severity of relapses and/or the number of new T2 or gadolinium-enhancing lesions is much higher than the pre-natalizumab activity. Patients with higher disability are particularly at risk as new relapses may result in further progression. Two to eight months after the last dose has been identified as the "high risk period" for disease reactivation. Close monitoring is essential to promptly detect clinical and/or radiological disease activity in order to change preventive therapy. Reintroduction of natalizumab therapy despite PML risk may be necessary if deemed the most clinically appropriate treatment.

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.

Switching Therapy: A baseline MRI should be completed prior to starting another disease modifying therapy post-natalizumab. For patients switching from another DMT to natalizumab please consult the relevant Summary of Product Characteristics for detailed information including washout periods.

Concurrent treatment with immunosuppressants: The safety and efficacy of natalizumab in combination with other immunosuppressive and antineoplastic therapies have not been fully established. Concurrent use of these agents with natalizumab may increase the risk of infections, including opportunistic infections, and is contraindicated. Physicians must evaluate each individual case to determine whether there is evidence of an immunocompromised state prior to commencing treatment with natalizumab.

Vaccinations
Live vaccines have not been studied. In randomised studies there was only a slightly slower and reduced humoral response to a neoantigen and no significant difference in the humoral response to a recall antigen.

Sodium content in natalizumab: TYSABRI® contains 2.3 mmol (or 52 mg) sodium per vial of medicinal product.

DRUG INTERACTIONS:

- Contraindicated in combination with other disease modifying treatments - beta-interferons or glatiramer acetate
- Current drug interaction databases should be consulted for more information.

SUPPORT RESOURCES:

Please note that this is for information only and does not constitute endorsement by the AHDMP
TYSABRI: Health Professional Guide. Available at https://www.hpra.ie/

ATC CODE:

Natalizumab L04AA23

REIMBURSEMENT CATEGORY:

National Drugs Management Scheme (NDMS)

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Neurologist experienced in the treatment of Multiple Sclerosis.

REFERENCES:

1. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med. 2006* Mar 2;**354**(9):899-910
2. Polman CH, Reingold SC, Banwell B, *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the MacDonald Criteria. *Ann Neurol* 2011; **69**:292-302
3. Rudick RA, Stuart WH, Calabresi PA, *et al.* SENTINEL Investigators (2006): Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med 2006.* Mar 2;**354(9)**:911-23
4. Butzkueven H, Kappos L, Pellegrini F, *et al*. Efficacy and safety of Natalizumab in multiple sclerosis: interim observational program results. *J Neurol Neurosurg Psychiatry* 2014;**0**:1-8
5. Hutchinson M, Kappos L, Calabresi P, *et al.* The efficacy of Natalizumab in patients with relapsing remitting multiple sclerosis: subgroup analysis of AFFIRM and SENTINEL. *J Neurol* 2009; **256**: 405-415
6. McGuigan C, Craner M, Guadagno J, *et al*. Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. *J Neurol Neurosurg Psychiatry* 2016;**87**:2 117-125
7. Plavina, T, Subramanyam, M, Bloomgren G , *et al*. (2014), Anti–JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol., 76: 802–812. doi:10.1002/ana.24286
8. Tysabri 300mg concentrate for solution for infusion. Accessed May 2019 Available at https://www.medicines.ie/medicines/tysabri-300mg-concentrate-for-solution-for-infusion-34084/
9. Zhovtis Ryerson L, Frohman TC, Foley J, *et al*. Extended interval dosing of natalizumab in multiple sclerosis. *J Neurol Neurosurg Psychiatry* . 2016; **87**:885–889.
10. Yamouta BI, Sahraianb MA, Ayoubia NE, *et al.* Efficacy and safety of natalizumab extended interval dosing. *Multiple Sclerosis and Related Disorders.* 2018; **24**:113-116.
11. Sangalli F, Moiola L, Ferrè L, *et al*. Long-term management of natalizumab discontinuation in a large monocentric cohort of multiple sclerosis patients. *Multiple Sclerosis and Related Disorders.* 2014; **3**:520–526
12. Tysabri 150 mg solution for injection in pre-filled syringe. Accessed July 2021. Available at

https://www.medicines.ie/medicines/tysabri-150-mg-solution-for-injection-in-pre-filled-syringe-35078/spc

Version	Date	Amendment	Approved By
2	9th July 2019	- "Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies)" added to Exclusions (previously under Cautions) - Exclusions updated to include patients previously administered cladribine - Recommendation to consider Varicella Zoster vaccination in antibody negative patients added - Frequency of anti-JCV antibody testing now every 6 months regardless of previous titres - Inclusion of the effects of IVIg and PLEX on interpretation of anti-JCV antibody results - Inclusion of possible extended dosing intervals from 4weekly to 5-8weekly if considered at risk of PML - Addition of risk of disease reactivation following cessation of natalizumab therapy; including "rebound activity" - Addition of recommendation to complete a baseline MRI prior to starting another disease modifying therapy post-natalizumab - Opportunistic infections section updated to include risk of Herpes infection including acute retinal necrosis (ARN) - Vaccinations section updated	
3		- Rewording of licensed indication to align with Summary of Product Characteristics. - Amendment of information for extended interval dosing as per Summary of Product Characteristics. - Reformatting in line with other AHDMP protocols	
4		- Addition of subcutaneous natalizumab pre-filled syringe formulation - Addition of advice on the switch in route of administration - Updating of information for extended interval dosing as per Summary of Product Characteristics for the subcutaneous natalizumab pre-filled syringe formulation.	
4.1		- Administrations changes in header to include document objective - Administrations changes in footer to include document developer, reviewers and approvers.	

Comments and feedback welcome at ahdmp@hse.ie