NDMP Multiple Sclerosis Treatment Protocol

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Natalizumab THERAPY

INDICATIONS FOR USE:

INDICATION	ICD10	Protocol Code
Natalizumab 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 activity despite existing therapy with at least one disease modifying therapy (DMT)	**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**

ELIGIBILTY:

- Indications as above
- Patient aged 18-65 (use with caution in patients outside of these age ranges)

EXCLUSIONS:

- Hypersensitivity to natalizumab or to any of the known excipients.
- Progressive Multifocal Leukoencephalopathy (PML)
- Combination with beta-interferon or glatiramer acetate
- Known active malignancies except for patients with cutaneous basal cell carcinoma

USE with CAUTION:

- Patients with increased risk for opportunistic infections namely immunocompromised patients including those receiving or still immunocompromised as a result of receiving previous therapies such as cyclophosphamide and mitoxantrone

- In patients who have received prior immunosuppression (azathioprine, methotrexate, cyclophosphamide, mitoxantrone etc.)
- 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
- JC Virus Antibody Index Status
- VZV Serology

Regular tests:

- FBC, U&E and LFTs every 3 months
  - JCV antibody negative – repeat blood for antibody index 6 monthly
  - JCV antibody positive (index <1.5) – repeat blood for antibody index 6 monthly
  - JCV antibody positive (index >1.5) – no requirement to repeat antibody index

- 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:

Drug	Dose	Route	Diluent & Rate	Cycle
Natalizumab	300mg	IV infusion	100ml 0.9% NaCl 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				

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). Elevated PML risk during natalizumab therapy is also associated with an increasing duration of natalizumab treatment.

DOSE MODIFICATIONS:

- No recommended dose modifications

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

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. Due to this increased risk of developing PML, the benefits and risks of natalizumab 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. If patients develop PML, natalizumab should be permanently discontinued.
In patients considered at high risk 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).

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 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.
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.

Switching Therapy: For patients switching from another DMT to natalizumab please consult the relevant SmPCs for detailed information.

Discontinuation of Natalizumab 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.

Hepatic Events: Spontaneous serious adverse reactions of liver injury 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. Natalizumab treatment should be discontinued for patients who have substantial liver injury.

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

DRUG INTERACTIONS:

- Contraindicated in combination with 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 NDMP

TYSABRI: Health Professional Guide. Available at http://www.hpra.ie/img/uploaded/swedocuments/edumat_auto_f4f7f753-c84b-4674-970b-bed64d19b40e.pdf

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 2 years of treatment, patients should be reinformed 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.

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 MS.

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, Confavreux C, Galetta SL, Radue EW, Lublin FD, Weinstock-Guttman B, Wynn DR, Lynn F, Panzara MA, Sandrock AW; 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. C McGuigan, M Craner, J Guadagno, R Kapoor, G Mazibrada, P Molyneux, R Nicholas, J Palace, O R Pearson, D Rog, C A Young. 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. 7. Plavina, T., Subramanyam, M., Bloomgren, G., Richman, S., Pace, A., Lee, S., Schlain, B., Campagnolo, D., Belachew, S. and Ticho, B. (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. 8. Tysabri 300mg concentrate for solution for infusion . Accessed Dec 2016 Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-

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Product_Information/human/000603/WC500044686.pdf

Version	Date	Amendment	Approved By

Comments and feedback welcome at ndmp@hse.ie