HSE Prescribing Protocol

Natalizumab (Tysabri®)

for

the Treatment of Relapsing Remitting Multiple Sclerosis (RRMS)

This document is intended for use by healthcare professionals only.

This guideline should be used in conjunction with the full prescribing and administration details in the Natalizumab (Tysabri®) Summary of Product Characterisics (SmPC) https://www.ema.europa.eu/en/documents/product-information/tysabri-epar-product-information_en.pdf[1]

INDICATIONS FOR USE[1]:

TREATMENT	INDICATION	ICD10	Protocol Code
Natalizumab (Tysabri®)	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 the* SmPC)	**G35**	**MS101a**
	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 ***OTHER INFORMATION*** section below.

TREATMENT[1]:

Two treatment options, intravenous route OR subcutaneous route

TREATMENT OPTION 1	DOSE	ROUTE	FREQUENCY
Natalizumab 300mg concentrate for solution for infusion	300mg	Intravenous infusion	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.			
TREATMENT OPTION 2	**DOSE**	**ROUTE**	**FREQUENCY**
Natalizumab 150mg solution for injection in pre-filled syringe	300mg (2 X 150mg pre-filled syringes)	Subcutaneous injection	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 should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions, in centres with timely access to MRI.

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- Administration is to be performed by a healthcare professional and patients must be monitored for early signs and symptoms of Progressive Multifocal Leukoencephalopathy (PML).
- Some patients may have been exposed to immunosuppressive medicinal products which have the potential to cause prolonged immunosuppression, even after dosing is discontinuted, Therefore the physician must confirm that such patients are not immunocompromised before starting treatment. See SmPC.
- Natalizumab subcutaneous injections administered by a healthcare professional outside a clinical setting (e.g. at home) may be considered for patients who have previously tolerated at least 6 doses of natalizumab well, i.e. who have not experienced hypersensitivity reactions. The decision for a patient to receive injections outside a clinical setting should be made after evaluation and recommendation by the specialised physician
- 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).
- Treatment with natalizumab is administered once every 28 days for up to 2 years. 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.
    - 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 SmPC and *Physician Information and Management Guidelines* for full information.

DOSE MODIFICATIONS:

Extended Interval Dosing: see SmPC and *Physician Information and Management Guidelines* for full information.

ELIGIBILTY CRITERIA:

- Patient has confirmed diagnosis of RRMS and is being treated as per the Indications 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)
- A *Patient Eligibility* form for natalizumab has been completed and added to the patient's clinical records. (A copy of the form is available from: https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/protocols/multiple-sclerosis.html)
- Patient must attend for medical appointments and investigations as determined by the clinical team.

EXCLUSION CRITERIA

Patients who do not meet the eligibility criteria above

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CONTRAINDICATIONS[1]:

- 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

PREGNANCY AND BREASTFEEDING:

See SmPC

BASELINE TESTS AND MONITORING

- Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.
- Discuss vaccination status with the patient, as appropriate. All vaccinations must be completed at least 6 weeks prior to treatment initiation.
- Ongoing monitoring for malignancy via national screening programs should be carried out– including standard breast cancer screening.

Table 2: Recommended baseline tests and schedule of assessments for patients treatment with Natalizumab

Assessment	Baseline	3 Monthly	6 Monthly
MRI	X[1]		X*
Record Prior Immunosuppression use	X		
Full Blood Count & Film	X	X	
EDSS Score	X	X	
Urea & electrolytes, Serum Creatinine	X	X	
Liver profile (including AST, GGT and albumin)	X	X	
Varicella Zoster Virus (VZV) Serology -	X[2]		
JCV antibody Index Status	X[3]		X[3]

[1] Within 3 months prior to treatment

[2] VZV vaccination of antibody-negative patients should be considered. VZV vaccination should be administered at least 6 weeks in advance of treatment.

[3] **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).

* 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 18 months treatment repeat MRI 6 monthly
- JCV antibody positive (index >1.5) – repeat MRI 4 monthly (modified protocol could be used for safety scans)

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SPECIAL WARNINGS AND PRECAUTION FOR USE:

See SmPC for full list

- 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.

STOPPING CRITERIA:

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 SmPC for further information on discontinuation of treatment.

ADVERSE EFFECTS:

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

OTHER INFORMATION:

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

DRUG INTERACTIONS:

See SmPC

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.

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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 4 weekly to 5-8 weekly if considered at risk of PML - Addition of risk of disease reactivation following cessation of natalizumab therapy; including "rebound activity"	

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		- 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.	
5.0	April 2024	- Routine two year review Updated to reflect standard AHDMP Template for Prescribing Protocols	

Comments and feedback welcome at ahdmp@hse.ie

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