# Local Natalizumab Treatment Protocol

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<tr>
<th><strong>1. New medicine name:</strong></th>
<th>Natalizumab 300mg concentrate for solution for infusion (Natalizumab®)</th>
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<td><strong>2. Licensed indication(s):</strong></td>
<td>Natalizumab is indicated for single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups; patients with high disease activity despite treatment with beta-interferon and patients with rapidly evolving severe (RES) RRMS.</td>
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| **3. Scottish Medicines Consortium advice:** | Natalizumab (Natalizumab®) is accepted for restricted use within NHS Scotland as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) only in patients with rapidly evolving severe RRMS defined by two or more disabling relapses in one year and with one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.  

In a post-hoc sub-group analysis of the pivotal trial, which included patients with rapidly evolving severe RRMS, it was associated with a significant reduction in the annualised relapse rate and the probability of sustained progression of disability over two years compared with placebo.  

**Medicines Advisory Group advice:** HOSPITAL ONLY (MS Clinic) |
| **4.* Prescriber details:** | To be prescribed in hospital only.  
Natalizumab therapy is to be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions, in centres with timely access to MRI. |
| **5.* Criteria for patient selection:** | Patients with relapsing remitting multiple sclerosis who have highly active disease i.e. rapidly evolving severe relapsing remitting MS defined as two or more disabling relapses in one year and with one or more gadolinium enhancing lesions on brain MRI or significantly increase in T2 lesion load compared with a previous MRI. Patients should have an EDSS in the range of 0-5. Patients should have failed on, or be unsuitable for, conventional disease modifying therapies (DMTs) and should be three months off any DMT. Patients should not have primary progressive or secondary progressive MS. |
| **6. Administration details:** | Patients treated with natalizumab must be given the special alert card. Resources for the management of hypersensitivity reactions and access to MRI should be available.  
Natalizumab must not be administered as a bolus injection. Add 15ml of Natalizumab concentrate (20mg/ml) to 100ml 0.9% NaCl solution for injection  
After dilution, 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.  

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 have had a 3 month treatment break. Some patients may have been exposed to immunosuppressive medications (e.g. mitoxantrone, cyclophosphamide, azathioprine). These drugs 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 with natalizumab. |
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 beyond 2 years are not available. Continued therapy beyond this time should be considered only following a reassessment of the potential for benefit and risk.

**Adults**
Natalizumab 300 mg is administered by intravenous infusion once every 4 weeks.

**Elderly**
Natalizumab is not recommended for use in patients aged over 65 due to a lack of data in this population.

**Children and adolescents**
Natalizumab is contraindicated in children and adolescents.

**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.

**Readministration**
The efficacy and safety of re-administration have not been established.

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<th>7. Contra-indications:</th>
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<td>Hypersensitivity to Natalizumab or to any of the excipients.</td>
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<td>Progressive Multifocal Leukoencephalopathy (PML).</td>
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<td>Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies, e.g. mitoxantrone or cyclophosphamide).</td>
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<td>Combination with beta-interferons or glatiramer acetate.</td>
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<td>Known active malignancies, except for patients with cutaneous basal cell carcinoma.</td>
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<th>8. Side-effects/cautions:</th>
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<td><strong>Progressive Multifocal Leukoencephalopathy (PML)</strong></td>
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<td>Use of natalizumab has been associated with an increased risk of PML.</td>
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<td>Before initiation of treatment with Natalizumab, a recent (usually within 3 months) Magnetic Resonance Image should be available. Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If new neurological symptoms occur, further dosing is to 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. If they are suggestive of PML, or if any doubt exists, further evaluation, including MRI scan (compared with pre-treatment MRI), CSF testing for JC Viral DNA and repeat neurological assessments, should be considered. Once the clinician has excluded PML, dosing of natalizumab may resume.</td>
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<td>The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive or psychiatric symptoms). 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.</td>
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<td>If a patient develops PML the dosing of natalizumab must be permanently discontinued. Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of natalizumab therapy may lead to similar stabilisation or improved outcome.</td>
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Hepatic Events
Spontaneous serious adverse reactions of liver injury have been reported. 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.

Other Opportunistic Infections
Other opportunistic infections have been reported with use of natalizumab, 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 natalizumab in patients without these co-morbidities cannot currently be excluded. Opportunistic infections were also detected in MS patients treated with natalizumab as a monotherapy.
Prescribers should be aware of the possibility that other opportunistic infections may occur during natalizumab therapy and should include them in the differential diagnosis of infections that occur in natalizumab-treated patients. If an opportunistic infection is suspected, dosing with natalizumab is to be suspended until such infections can be excluded through further evaluations.
If a patient receiving natalizumab develops an opportunistic infection, dosing of natalizumab must be permanently discontinued.

Educational guidance
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 natalizumab.

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, but 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. Resources for the management of hypersensitivity reactions should be available. Discontinue administration of natalizumab and initiate appropriate therapy at the first symptoms or signs of hypersensitivity.
Patients who have experienced a hypersensitivity reaction must be permanently discontinued from treatment with natalizumab.

Concurrent or prior 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.
Patients with a treatment history of immunosuppressant medications, including cyclophosphamide and mitoxantrone, may experience prolonged immunosuppression and therefore may be at increased risk 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 with natalizumab.
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 natalizumab.

Immunogenicity
Disease exacerbations or infusion related events may indicate the development of antibodies against natalizumab. In case these events occur the presence of antibodies


should be evaluated and if these remain positive in a confirmatory test after 6 weeks, treatment should be discontinued as persistent antibodies are associated with a substantial decrease in the effectiveness of natalizumab and an increased incidence of hypersensitivity reactions.

**Stopping 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 drugs 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 medicines 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.

**Monitoring - response to treatment:**

The therapeutic effect of natalizumab shall be monitored every month. Patients will have relapse rate documented and have an annual EDSS score. Neutralising antibodies will be tested every three months.

Patients will be stopped under the following circumstances:

1. Development of secondary progressive disease
2. Two significant attacks in one year
3. EDSS score of greater than 5.5
4. Persistently positive neutralising antibodies
5. Development of progressive multifocal leukoencephalopathy
6. Development of substantial liver injury

Data on the safety and efficacy of natalizumab beyond 2 years are not available. Continued therapy beyond this time should be considered only following a reassessment of the potential for benefit and risk.

**Monitoring – treatment safety:**

Patients should have a full blood count and liver function test prior to commencement of therapy and at regular monthly intervals during treatment. The following undesirable effects shall be monitored:

- **Infections and infestations**
  - Urinary tract infection
- **Immune system disorders**
  - Urticaria
  - Hypersensitivity
- **Nervous system disorders**
  - Headache
- **Gastrointestinal disorders**
  - Vomiting
- **Musculoskeletal and connective tissue disorders**
Musculoskeletal and connective tissue disorders

Arthralgia

General disorders and administration site conditions

Rigors
Pyrexia
Fatigue

Infusion reactions
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 natalizumab. Hypersensitivity reactions usually occurred during the infusion or within the 1-hour period after the completion of the infusion.

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.

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. Early post-marketing experience included one fatal case of herpes encephalitis. See section 4.4. The majority of patients did not interrupt Natalizumab therapy during infections and recovery occurred with appropriate treatment.

In clinical trials, cases of PML have been reported. PML usually leads to severe disability or death. In pivotal clinical trials, two cases, including one fatality, occurred in MS patients who were being treated with concomitant interferon beta-1a therapy for more than 2 years. In another trial, one patient with Crohn's disease, who had a long history of treatment with immunosuppressants and associated lymphopenia also developed PML and died.

Although each case of PML occurred in patients either with concomitant use of immune modulating drugs or with evidence of immunosuppression, it remains possible that the risk of PML is associated with natalizumab alone.

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.

**Effects on laboratory tests**

Natalizumab treatment 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. During treatment with natalizumab, 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 natalizumab and the changes were not associated with clinical symptoms.

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<th>11.*</th>
<th><strong>Written by:</strong> Dr J O’Riordan</th>
<th><strong>Date:</strong> 14 Dec 2007</th>
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<td><strong>Approved by:</strong> Dr R Swingler</td>
<td><strong>Date:</strong> 18 Jan 2008</td>
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<td><strong>Reviewed and updated by:</strong> Fiona Mc Grehan and Dr J O’Riordan</td>
<td><strong>Date:</strong> 10 Nov 2008</td>
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| 12.* | **Review date:** Dec 2009 |

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