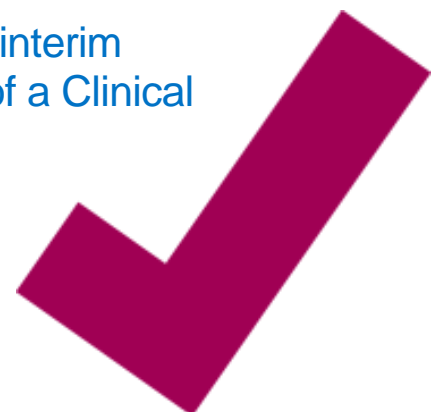


**Urgent Clinical
Commissioning Policy
Statement: Natalizumab-
induced Progressive
Multifocal
Leukoencephalopathy in
relation to Immune
Reconstitution
Inflammatory Syndrome
in Multiple Sclerosis (all
ages)**

NHS England Reference: 170040P

A clinical commissioning policy statement is an interim commissioning position pending the formation of a Clinical Policy.



1 Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of this policy statement, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

In the interests of delivering an urgent interim position a rapid initial equality impact assessment has been carried out and a full equality health impact assessment will be undertaken when a clinical commissioning policy is published to replace this document.

2 Background

Natalizumab-induced Progressive Multifocal Leukoencephalopathy (PML) in relation to Immune Reconstitution Inflammatory Syndrome (IRIS) in Multiple Sclerosis (MS).

Maraviroc is used in Human Immunodeficiency Virus (HIV) positive patients as an antiretroviral drug. It has been used in a few cases of PML-IRIS MS patients to help with the clearance of John Cunningham (JC) virus.

PML-IRIS in patients with Relapsing Remitting Multiple Sclerosis (RRMS) is a new condition related to JC virus reactivation/infection due to Natalizumab therapy. In 23% of cases the outcome is death. Of the survivors, 80% of patients have moderate or severe neurological impairment, and 20% have mild impairment. There have not been any clinical trials in this area to guide treatment.

Maraviroc is a CCR5 chemokine receptor antagonist that is approved for the treatment of HIV infection. There is limited data in regards to the utility of the drug.

Treatment of PML-IRIS is mainly empirical; as of today, there are no randomized controlled trials (RCTs) to support antiviral or immune-modulating therapy in this condition. Since oedema and inflammation appear on the Magnetic Resonance Imaging (MRI) scans, patients are commonly treated with intravenous and oral steroids.

3 Evidence Summary

NHS England has considered the evidence submitted as part of the preliminary policy proposal to establish an urgent clinical commissioning policy statement, including the clinical criteria for initiating and discontinuing the intervention. This includes the most clinically impactful publications, identified using a literature search strategy defined by the clinical lead. These publications are summarised below.

Publication 1 (Hodecker et al 2017)

Case 1: A 34-year-old man with RRMS (an Expanded Disability Status Scale (EDSS) score of 3.5) had been treated with natalizumab for 3 years without previous immunosuppression. Treatment was stopped because of a high JCV antibody index (3.21 in July 2014). At 12 months after diagnosis of PML-IRIS and 6 months after start of maraviroc, the EDSS score was 4.0. PML-IRIS lesions did resolve, and no new MS disease activity was detectable.

Case 2: A 40-year-old man with RRMS, an EDSS score of 0, had received natalizumab treatment for 4 years as a second-line treatment following β -interferons. The patient had been JCV antibody-positive. Treatment with maraviroc was started at a dose of 300 mg twice daily. While the patient remained asymptomatic, JCV DNA in the CSF increased to 330 copies/mL with increased gadolinium enhancement on MRI. 11 months after the initial diagnosis of PML, multiple disseminated contrast-enhancing lesions in the cerebellum were still detectable on MRI, indicating persisting PML-IRIS. No new MS disease activity was noted, and the clinical condition reached pre-PML status.

This study is an observational study without controls and provides limited evidence on the clinical effectiveness of the treatment. Further studies are warranted for evidence-based recommendations on the management of patients with early-identified natalizumab-associated PML.

Publication 2 (Bsteh et al 2017)

This study is a case report of a 55-year-old caucasian HIV-negative man diagnosed with relapsing-remitting MS in 2013 and an Expanded Disability Status Scale (EDSS) score of 2.0 had received 20 infusions of natalizumab over 21 months without a history of prior immunotherapy. John Cunningham-virus (JCV) antibodies were positive at the initiation of treatment (index: 0.4). Natalizumab was then discontinued because of an increase of anti-JCV antibody index (2.6) and switched to fingolimod following a 2-month washout period. Brain MRI performed 2 months before the initiation of fingolimod showed no signs of MS disease activity or progressive multifocal leukoencephalopathy (PML).

The patient was first admitted to hospital 10 days after fingolimod initiation. Oral maraviroc (300 mg twice daily) was initiated 6 days after admission. After 25 weeks of maraviroc treatment, JCV DNA was no longer detectable in the CSF.

Maraviroc was continued and well tolerated at a stable dose.

This is an observational study reporting a single case which provides limited evidence of clinical effectiveness of maraviroc in the treatment of PML-IRIS in MS.

4 Commissioning Position

Rationale for a clinical commissioning policy statement

The use of Maraviroc to treat Natalizumab-induced PML-IRIS in relation to RRMS currently has an evidence base limited to very small observational studies. This indication and treatment is currently seen as experimental.

Clinical commissioning position

Based on limited evidence and the lack of any evidence based clinical support for this drug to be used for this indication, NHS England has concluded that there is not sufficient evidence to support for the routine commissioning of this treatment for the indications listed.

Clinical commissioning policy development plan

It has been assessed that the development of a full policy is not needed at this time as there is currently little evidence into its effectiveness for this indication.

5 Mechanism for funding

Not routinely commissioned.

6 Date of policy statement approval and review

The policy statement is effective from March 2018.

A clinical commissioning policy is not planned to be developed at this stage. If a clinician, supported by peers, seeks a reappraisal by the Specialised Services Clinical Panel then a new Preliminary Policy Proposition should be submitted. For guidance email england.specialisedcommissioning@nhs.net.

7 References

Hodecker, S. C., Stürner, K. H., Becker, V., Elias-Hamp, B., Holst, B., Friese, M. A., & Heesen, C. (2017). Maraviroc as possible treatment for PML-IRIS in natalizumab-treated patients with MS. *Neurology Neuroimmunology & Neuroinflammation*, 4(2), e325.

Bsteh, G., Auer, M., Iglseder, S., Walchhofer, L.-M., Langenscheidt, D., Koppi, S., Berger, T. (2017). Severe early natalizumab-associated PML in MS: Effective control of PML-IRIS with maraviroc. *Neurology Neuroimmunology & Neuroinflammation*, 4(2), e323.