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Dear Healthcare Professionals,



DEPARTMENT OF HEALTH
DRUG OFFICE
DRUG REGISTRATION AND
IMPORT/EXPORT CONTROL DIVISION
3/F., Public Health Laboratory Centre,
382 Nam Cheong Street, Kowloon, Hong Kong

19 April 2016

Natalizumab (Tysabri▼): progressive multifocal leukoencephalopathy: updated advice to support early detection

Your attention is drawn to the Medicines and Healthcare products Regulatory Agency's (MHRA) announcement regarding updated advice on Natalizumab (Tysabri) to support early detection of progressive multifocal leukoencephalopathy (PML).

Natalizumab (Tysabri) is a single disease-modifying therapy for adults with multiple sclerosis who have high disease activity despite treatment with beta-interferon, or who have rapidly evolving severe relapsing remitting disease.

Natalizumab is associated with a risk of PML— a rare, progressive, and demyelinating disease of the central nervous system that can be fatal. It is caused by activation of John Cunningham virus (JCV), which usually remains latent and typically only causes PML in immunocompromised patients.

Up to August 2015, there had been 582 reports worldwide from clinical practice of PML in patients receiving natalizumab. Up to 30 March 2016, the MHRA had received 33 Yellow Card reports of PML in patients receiving natalizumab in the UK. Evidence from these reports and several studies has led to new advice to reduce the risk of PML as listed below.

Recent analyses suggest that earlier detection of PML is associated with improved outcomes. Cases of asymptomatic PML, diagnosed based on MRI scans and positive JCV DNA in the cerebrospinal fluid, have been reported. PML which is clinically asymptomatic at diagnosis has more localised or unilobar lesions on MRI scans compared with symptomatic patients. Occasionally, particularly in patients with small lesions, exclusively grey matter involvement of PML has been observed on MRI scans.

Note that these analyses have important potential limitations, including lead time bias and length time bias. There was also information missing on MRI frequency in symptomatic PML cases, preventing comparison with PML cases asymptomatic at onset.

Therefore the risk-proportionate MRI screening protocol for PML described is recommended for patients receiving natalizumab. It is also important that patients do not have any signs or symptoms of PML before switching to other disease-modifying treatments.

The risk of PML in patients receiving natalizumab is already known to be higher in patients who are serum anti-JCV antibody positive, have had immunosuppressant therapy, and have been receiving natalizumab for a long time (especially for more than 2 years).

Recent data show that in patients who have not had immunosuppressant therapy and are serum anti-JCV antibody positive, the risk of PML rises with increased serum anti-JCV antibody index.

Therefore, the following groups of patients have been defined as being at high risk of PML:

- those who have all three risk factors for PML (ie immunosuppressant therapy, serum anti-JCV antibody positive, and more than 2 years of natalizumab exposure)
- those who have not had immunosuppressant therapy but have a high serum anti-JCV antibody index and more than 2 years of natalizumab exposure

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aspire to be an internationally renowned public health authority*

For these high-risk groups, consider the extra precautions listed in the ‘during natalizumab treatment’ section listed below.

The MHRA advised healthcare professionals of the following:

1) Before starting natalizumab treatment

New advice:

- Perform a baseline quantitative serum anti-JCV antibody test—including the index value—to support risk stratification for progressive multifocal leukoencephalopathy (PML)

Reminder of previous advice:

- Perform a baseline cranial MRI scan as a reference, usually within 3 months of starting natalizumab treatment
- Counsel patients and carers on the risk of PML — an updated Treatment Initiation Form will be available in due course
- Advise patients and carers on symptoms to watch out for and to get medical advice urgently if they occur

2) During natalizumab treatment

New advice:

- Perform a quantitative serum anti-JCV antibody test—including the index value—every 6 months for the patients specified in the algorithm in the MHRA website
- For high-risk patients, consider the following extra precautions:
 - more frequent MRI screening for PML, such as every 3–6 months using an abbreviated protocol (FLAIR, T2-weighted, and DW imaging): earlier detection of PML in asymptomatic patients may be associated with improved PML outcome
 - If PML is suspected, extend the MRI protocol to include contrast-enhanced T1-weighted imaging and consider testing for JCV DNA in the cerebrospinal fluid using ultrasensitive polymerase chain reaction (PCR)

Reminder of previous advice (for all patients):

- If PML is suspected at any time, stop natalizumab treatment and investigate appropriately until PML has been excluded
- Perform a quantitative serum anti-JCV antibody test—including the index value—for any patient with unknown antibody index (all patients should be tested at least once)
- Perform a full cranial MRI scan at least yearly for the entire duration of treatment, to have up-to-date reference images
- Monitor patients for signs and symptoms or appearance of new neurological dysfunction (eg motor, cognitive, or psychiatric symptoms), bearing in mind that PML can present with features similar to multiple sclerosis
- Consider PML in the differential diagnosis of any patient presenting with neurological symptoms or new brain lesions in their MRI scan – cases of asymptomatic PML, diagnosed based on MRI scans and positive JCV DNA in the cerebrospinal fluid, have been reported
- After 2 years of treatment, remind patients of the risk of PML with natalizumab using the updated Treatment Continuation Form, which will be available in due course

3) After stopping natalizumab treatment:

New advice:

- Advise patients and carers to continue to watch out for signs and symptoms of PML for 6 months after the last dose—use the new Treatment Discontinuation Form, which will be available in due course, to aid this discussion
- Continue the same monitoring protocol for 6 months after the last dose, as PML has been reported during this time

Please refer to the MHRA's website for details:

<https://www.gov.uk/drug-safety-update/natalizumab-tysabri-progressive-multifocal-leukoencephalopathy-updated-advice-to-support-early-detection>

In Hong Kong, there is one registered pharmaceutical product containing natalizumab, namely Tysabri Concentrate for Solution for Infusion 300mg (HK-61519) which is registered by UCB Pharma (Hong Kong) Limited, and is a prescription only medicine. Related news was previously issued by the EMA, and was posted on the Drug Office website on 12 October 2015, 13 February 2016 and 27 February 2016. Letters to local healthcare professionals to draw their attention was issued on 15 February 2016. The local package insert of the product has already included the warning on PML. So far, DH has not received any adverse drug reaction case related to natalizumab. As previously reported, the matter, including the above MHRA's updated advices, will be discussed by the Registration Committee. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Pharmacovigilance Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": <http://www.drugoffice.gov.hk/adr.html>. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,



(Grant NG)

for Assistant Director (Drug)