Drug Safety Update

MHRA

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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Contents

The **Medicines and Healthcare products Regulatory Agency** is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The **Commission on Human Medicines** gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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This month, further information is available to support safer use of modafinil, now restricted to use only in the treatment of narcolepsy, including: cautions for use; criteria for stopping treatment; and monitoring requirements during treatment—see article A1.

We have previously advised that the risk of progressive multifocal leukoencephalopathy associated with natalizumab increases with treatment duration, especially beyond 2 years (see Drug Safety Update March 2010; http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON091088). There is now further information that the risk of developing PML is increased in patients who have had previous immunosuppressant therapy (eg, azathioprine, cyclophosphamide, mitoxantrone, and methotrexate). Prescribers should ensure that patients are aware of this risk—see article A2 for further information.

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Drug safety advice

A1 Modafinil (Provigil): information to support safer use; now restricted to narcolepsy

Following European-wide restriction of use of modafinil to the narcolepsy indication, further information is available to support safer use, including: cautions for use; criteria for stopping treatment; and monitoring requirements during treatment

Modafinil (Provigil) is a wakefulness-promoting agent that acts on the CNS. It is indicated for the treatment of excessive sleepiness in adults with narcolepsy, with or without cataplexy. The recommended starting dose is 200 mg a day.

August 2010 Drug Safety Update: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON090901

A recent European review of the benefits and risks of modafinil has recently been completed, and information about the restricted use of this drug as a result of this review was published in the August 2010 issue of Drug Safety Update.

Also as a result of the review, further information and advice is available to support safer use of modafinil.

New information and advice for healthcare professionals:

Product information advises against use in the following groups:

- Those with uncontrolled hypertension or cardiac arrhythmias
- Children up to 18 years old
- Women who are pregnant or breastfeeding

Treatment discontinuation:

- Modafinil should be discontinued and not restarted in cases of:
  - Serious skin or hypersensitivity reactions
  - Psychiatric disorders such as suicidal ideation

Monitoring during treatment:

- A baseline electrocardiogram should be done before treatment initiation. Patients with abnormal findings should be further evaluated by specialists before modafinil treatment can be initiated
- Cardiovascular function—especially blood pressure and heart rate—should be monitored regularly. Modafinil should be discontinued in patients who develop arrhythmia or moderate to severe hypertension, and should not be restarted until the condition has been adequately evaluated and treated

Cautions for use:

- Modafinil should be used with caution in patients with a history of:
  - Psychosis, depression, or mania
  - Abuse of alcohol, drugs, or illicit substances
- Such patients should be monitored closely and advised to report any suspected adverse behaviours or thoughts. Patients should be assessed immediately and treatment stopped if appropriate

Further information:

See letter for healthcare professionals: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON111461

BNF section 4.4 CNS stimulants and drugs used for attention deficit hyperactivity disorder: http://bnf.org/bnf/bnf/current/68990.htm

Advice on treatment cessation

Modafinil is no longer indicated for shift-worker sleep disorder and obstructive sleep apnoea. Patients should be advised to contact their doctor if they are unsure as to whether they should discontinue modafinil treatment. Although there is no need to stop treatment immediately, patients who wish to stop can do so at any time.

Reporting of suspected adverse reactions

Suspected adverse reactions to modafinil should be reported promptly via the Yellow Card Scheme at www.yellowcard.gov.uk.

Article citation: Drug Safety Update March 2011 vol 4, issue 8: A1.

A2 Natalizumab (Tysabri▼): risk of progressive multifocal leukoencephalopathy is increased in patients who have had previous immunosuppressant treatment

The risk of developing progressive multifocal leukoencephalopathy (PML) associated with natalizumab is increased in patients who have had previous immunosuppressant therapy. Prescribers should ensure that patients are aware of this updated advice to help minimise the risk of PML

Natalizumab (Tysabri▼) is a single disease-modifying therapy for patients with multiple sclerosis who have high disease activity despite treatment with beta-interferon, or who have rapidly evolving severe relapsing remitting disease. It is the first agent in its class for multiple sclerosis.

The standard dose is 300 mg natalizumab by intravenous infusion (over about 1 hour) once every 4 weeks. Patients should be observed during infusion and for 1 hour after for signs and symptoms of hypersensitivity.

Risk of progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare, progressive, and demyelinating disease of the CNS that may be fatal. It is caused by activation of JC virus, which usually remains latent and typically only causes PML in immunocompromised patients. The factors leading to activation of the latent infection are not fully understood. JC virus is widespread in the general population, including patients with multiple sclerosis, and the prevalence of antibodies increases with age.

Summary of Product Characteristics: http://www.medicines.org.uk/EMC/medicine/18447/SPC/TYSABRI+300+mg+concentrate+for+solution+for+infusion/

See Drug Safety Update March 2010: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON091088

PML was identified as a safety risk associated with natalizumab at the time of licensing, and information on how to minimise this risk has been included in the Summary of Product Characteristics.

The risk of PML increases with treatment duration, especially beyond 2 years.

A recent analysis of patients diagnosed with PML suggests that the risk of PML is increased in patients who have been treated with an immunosuppressant (eg, azathioprine, cyclophosphamide, mitoxantrone, and methotrexate) before receiving natalizumab. This analysis used data from an ongoing observational study (TYGRIS—Tysabri Global Observational Program In Safety) to compare the risk of PML in patients who were either treated or not treated with immunosuppressants before starting natalizumab.

New advice for healthcare professionals:

- Patients should be advised that the risk of PML is greater if they have previously taken an immunosuppressant

Previous advice remains:

- Patients should be advised that the risk of PML increases with duration of treatment with natalizumab, especially beyond 2 years
- Patients should be informed about the risks via a treatment initiation /continuation form and updated patient information leaflet
- Natalizumab should be promptly discontinued if PML is suspected, with subsequent appropriate evaluation including standardised MRI and lumbar puncture
- Further information for prescribers is available in the Physician Information and Management Guidelines (for further information, see a letter sent to healthcare professionals in January 2011)

Letter sent to healthcare professionals January 2011: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON106073

Further information:

BNF section 8.2.4 Other immunomodulating drugs: http://bnf.org/bnf/bnf/current/129973.htm

Reporting of suspected adverse reactions

Natalizumab is under intensive monitoring by the MHRA, and healthcare professionals are reminded to report suspected adverse reactions promptly via the Yellow Card Scheme at www.yellowcard.gov.uk.

Article citation: Drug Safety Update March 2011 vol 4, issue 8: A2.