

Drug Safety Update



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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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.



The MHRA is accredited by NHS Evidence to provide Drug Safety Update. Further information on the accreditation can be found on the NHS Evidence portal <http://www.evidence.nhs.uk/Accreditation/>

A Europe-wide review of natalizumab (Tysabri ▼) for patients with multiple sclerosis has led to new recommendations to help minimise the risk of the rare but serious CNS disease, progressive multifocal leukoencephalopathy (PML). The risk of developing PML increases with duration of treatment; patients should be informed about the risks of natalizumab both before treatment and again after 2 years. The balance of benefits and risk should be reconsidered at this time (see p 2 for further details).

Also this month, we give advice regarding the risk of congenital abnormalities with the use of the selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine in pregnancy. Epidemiological data from studies on fluoxetine suggests that infants of mothers exposed to fluoxetine during the first trimester of pregnancy may be at a small increased risk of developing congenital cardiac defects, similar to that seen with paroxetine. When treating depression during pregnancy, prescribers should consider this potential increased risk in the context of the benefits of treatment (see p 4 for further details).

Finally this month, we are pleased to announce that Drug Safety Update has been accredited by NHS Evidence (see <http://www.evidence.nhs.uk>). The NHS Evidence Accreditation Scheme recognises organisations that demonstrate high standards in producing health or social care guidance. Drug Safety Update articles can now also be retrieved from NHS Evidence—see p 5 for more information.

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Natalizumab (Tysabri ▼): risk of progressive multifocal leukoencephalopathy increases after 2 years of therapy

Keywords: natalizumab, Tysabri (▼), progressive multifocal leukoencephalopathy, PML, multiple sclerosis, immune reconstitution inflammatory syndrome, IRIS

The risk of developing progressive multifocal leukoencephalopathy (PML) with natalizumab increases after 2 years of therapy. Patients with multiple sclerosis should be informed of the risk before treatment, and again after 2 years. The risk of developing PML beyond 3 years of treatment is currently unknown. Product information for healthcare professionals and patients is being updated with the latest information

Natalizumab (Tysabri ▼) is a 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 for multiple sclerosis in its class.

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 and the prevalence of antibodies increases with age.

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 (SPC).

Up to 20 Jan, 2010, 31 cases of PML have been reported worldwide in patients with multiple sclerosis receiving natalizumab, eight of which were fatal. No cases of PML have been reported in the UK for this drug. Approximately 66 000 people have been exposed worldwide to natalizumab up to Jan 20, 2010.

23 of the 31 confirmed cases reported to date occurred in patients exposed to natalizumab for 2 years or more. The reporting rate is equivalent to around one to two cases of PML for every 1000 patients treated with Tysabri (▼) for 2 or more years.

Risk of immune reconstitution inflammatory syndrome (IRIS)

Plasma exchange/immunoabsorption (PLEX/IA) has often been used to reduce natalizumab levels more quickly when PML has been identified. Use of PLEX/IA accelerates the development of immune reconstitution inflammatory syndrome (IRIS) in the following days to weeks. IRIS is caused by an enhanced viral clearance by the immune system, and can lead to worsening of neurological symptoms.

Monitoring for development of IRIS and appropriate treatment of the associated inflammation during recovery from PML should be undertaken. Treatment could be started with a high-dose systemic steroid at the first signs of IRIS. Patients with signs and symptoms suggestive of IRIS should receive intensive care monitoring. Product information is being updated in line with this information.

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For further information on a worldwide postmarketing study (the Tysabri Observational Program) currently recruiting to assess the long-term safety and effectiveness of natalizumab, see <http://clinicaltrials.gov/ct2/show/NCT00493298?term=NCT00493298&rank=1>. TYGRIS (Tysabri Global Observational Program In Safety) is an ongoing observational study (not recruiting), details of which are available at <http://clinicaltrials.gov/ct2/show/NCT00483847?term=NCT00483847&rank=1>

For further information, see a letter sent to healthcare professionals 17 Feb 2010: <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsoonthesafetyofmedicines/index.htm>

See www.yellowcard.gov.uk

Advice for healthcare professionals:

- Patients should be informed about the risks of natalizumab both before treatment and again after 2 years. The balance of benefits and risk should be reconsidered at this time
- Forms will become available for patients to confirm at both time points that they have been informed of the risks. Additionally, updated patient 'alert cards' will be available
- An MRI is recommended within 3 months before initiation of treatment with natalizumab and annually thereafter, in order to provide updated baseline imaging
- Continued clinical vigilance for signs or symptoms suggestive of PML is essential (eg, impaired cognition, visual disturbances, hemiparesis, altered mental state, or behavioural changes). Patients, carers, partners, and families should be aware of these
- Natalizumab should be promptly discontinued if PML is suspected, with subsequent appropriate evaluation including a standardised MRI scan and lumbar puncture
- Patients treated for PML should be closely monitored for the development of IRIS. Those with signs and symptoms suggestive of IRIS should receive intensive care monitoring
- Where possible, patients should be treated with natalizumab as part of a national registry or postmarketing study

Reporting of suspected adverse reactions

Natalizumab is under intensive monitoring (▼) by the MHRA, and healthcare professionals are reminded to report all suspected adverse reactions promptly via the Yellow Card Scheme.

Fluoxetine: possible small risk of congenital cardiac defects

Keywords: fluoxetine, selective serotonin reuptake inhibitors, SSRIs, antidepressants, congenital cardiac defects

Recent epidemiological evidence suggests a possible small increased risk of congenital cardiac defects in association with fluoxetine in early pregnancy, similar to that seen with paroxetine. There are insufficient data to draw conclusions on whether there is a similar risk for other SSRIs. The potential risks should be considered in the context of the benefits of treatment

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Fluoxetine (brand leader Prozac) is a commonly used antidepressant belonging to the selective serotonin reuptake inhibitor (SSRI) class of medicines. Depressive symptoms and major depressive disorders occur in pregnant women with prevalence rates ranging from 7% to 20%.^{1,2} Untreated depression in pregnancy is associated with a variety of adverse outcomes, including low birth weight, preterm delivery, and lower Apgar scores.^{3,4} It is estimated that 2.3% of pregnant women per year are exposed to SSRI antidepressant therapy.⁴

An analysis of epidemiological data from seven cohort studies^{5–11} provided a risk estimate of 1.08 (0.84–1.39) for all congenital malformations with fluoxetine use. Analysis of data from five studies^{5,7–8, 10–11} out of the seven gave a risk estimate of 1.43 (0.83–2.47) for congenital cardiac defects (data are odds ratios and 95% confidence intervals). The results suggest that fluoxetine is not associated with a risk of non-cardiac defects, and that any increased risk of malformations appears to be driven by a possible excess cardiac risk. The cardiac defects reported in the studies included in the meta analysis were varied, and ranged in severity from reversible ventricular septal defects to transposition of the great vessels.

The background incidence of congenital cardiac defects is approximately 1/100. The meta-analysis results for fluoxetine are consistent with an increased absolute risk to less than 2/100 pregnancies. The current evidence indicates that the risk of congenital cardiac defects for fluoxetine is similar to that for paroxetine. The mechanism is unknown and it is possible that the effects may be a class-related phenomenon, however data are insufficient at present to issue advice about the risk with other SSRIs.

The current Summary of Product Characteristics (SPCs) and Patient Information Leaflets (PILs) are being revised to reflect this information for fluoxetine-containing products.

Advice for healthcare professionals:

- When prescribing fluoxetine to treat depression during pregnancy, prescribers should be aware that there may be a small increased risk of congenital cardiac defects in infants exposed in early pregnancy, similar to that seen with paroxetine
- There are insufficient data to draw conclusions on the risk of congenital anomalies with other SSRIs, but the possibility of a class effect cannot be excluded
- The potential increased risk should be considered in the context of the benefits of treating depression in pregnancy

Stop press

Sirolimus: different immunoassays for therapeutic drug monitoring—risk of incorrect dose adjustment

Sirolimus (Rapamune ▼) is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant.

Optimal therapy requires therapeutic drug concentration monitoring in all patients. Adjustments to the targeted therapeutic dose range of sirolimus must only be made with a detailed knowledge of the specific assay used to measure the drug concentration in the patient.

Currently, sirolimus whole-blood concentrations are measured using either the reference assay high performance liquid chromatography (HPLC), or an immunoassay. Switching between different immunoassays, or between an immunoassay and HPLC, in a single patient can lead to clinically significant differences in results, and therefore, incorrect dose adjustments. This, in turn, may have potential adverse consequences, such as allograft rejection if drug exposure is too low or toxic side effects if exposure is too high.

A letter has been sent to healthcare professionals in February 2010 to encourage prescribers to regularly contact their laboratory and ascertain whether the assay used recently has been changed, and whether there have been any changes to the laboratory's reference range.

For further information, see a letter sent to healthcare professionals on 8 Feb, 2010:

<http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm>

Other information from the MHRA

Drug Safety Update gains NHS Evidence accreditation

Drug Safety Update has been accredited by NHS Evidence, the website which provides rapid access to evidence, guidance, and government policy on health and social care. The NHS Evidence Accreditation Scheme recognises organisations that demonstrate high standards in producing health or social care guidance. An accreditation mark against a search result reassures users that the information has been constructed to a high standard.

The accreditation evaluation found that the processes which underpin Drug Safety Update articles are robust and comprehensive; it also found that the recommendations in our guidance are clear, specific, unambiguous, and timely.

Drug Safety Update articles will now be available through NHS Evidence at <http://www.evidence.nhs.uk>; they will be displayed with the accreditation mark (left) and appear near the top of relevant searches.



MHRA conference for doctors in training:

“Unusual Suspects—Patient Safety and the Regulation of Drugs and Medical Devices”, May 26 2010, The Royal York Hotel, York

Following on from the successful conference hosted in 2009 in conjunction with the National Institute for Clinical Excellence (NICE), this event will provide trainee doctors with insight into the work of the MHRA and its important role in protecting public health.

This event aims to stimulate interest in the intellectual challenges of regulation,

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For more information and to register for this event, visit:

www.mhra.gov.uk/ConferencesLearningCentre/Conferences/CON065793

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help junior doctors to understand how we learn from adverse events, and how to improve patient safety through reporting. It will also explain how national guidelines are formulated and introduced, while also providing a background to regulatory framework that underpins medicines and medical devices in the UK.

Patient Information Leaflet of the month: Human Varicella-Zoster Immunoglobulin vaccine

Access PIL of the month at
[http://www.mhra.gov.uk/Howweregulate/
Medicines/Labelspatientinformationleafle
tsandpackaging/Patientinformationleaflet
\(PIL\)ofthemonth/index.htm](http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleafletsandpackaging/Patientinformationleaflet(PIL)ofthemonth/index.htm)

Patient information leaflets (PILs) are improving in quality as a result of new legal obligations for manufacturers to test the documents on potential patients. Testing makes sure that the presentation of the information enables patients to find and understand key messages for safe use about the medicine within the PIL and thereby enables them to use the medicine safely and effectively. To promote this new initiative, we are publishing a series of examples of best practice on our website. The latest in the series is for Human Varicella-Zoster Immunoglobulin which is used to protect against infection by the varicella-zoster virus, which causes chickenpox and shingles. The leaflet design uses good navigation tools and in testing was found to be well received by patients.

Read more about the Commission on Human Medicines, including summaries of minutes from meetings, at www.mhra.gov.uk/Committees/Medicinesadvisorybodies/CommissiononHumanMedicines

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