# Drug Safety Update

## Latest advice for all medicines users

The monthly newsletter from the **Medicines and Healthcare products Regulatory Agency** and the **Commission on Human Medicines**

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## Contents

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In the final issue of Drug Safety Update for 2008, our end-of-year quiz highlights some of the important safety topics we have covered in the past year: interactions with statins (particularly the new information for atorvastatin); psychiatric side-effects associated with the smoking-cessation drug varenicline; the cardiovascular safety of rosiglitazone for diabetes; and the serious risk of unintentional overdose with fentanyl pain-relief patches. Be sure to try our quiz on p 6 to reflect on your current safety knowledge; answers are on p 10.

Safer prescribing and use of medicines go hand-in-hand with Yellow Card reporting, and we would like to thank all of you who have completed Yellow Cards this year to tell us about a suspected adverse reaction. Our Yellow Card Scheme update this month reflects on some important enhancements to the Scheme in 2008 (p 5).

Our safety advice this month focuses on two risks. First, there have been cases of progressive multifocal leukoencephalopathy with the monoclonal antibodies rituximab and efalizumab. Please read our guidance on p 3 to try to help minimise this risk. Second, although nitrous oxide has a very good safety profile in normal use under the supervision of a healthcare professional, we would like to remind you that prolonged use may lead in rare cases to megaloblastic anaemia and neurological toxic effects (myelopathy) due to inactivation of vitamin B12 (p 2).

The Drug Safety Update team here at the MHRA would like to wish you a very happy festive season and a healthy and successful 2009.

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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 safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

# Drug safety advice

## Nitrous oxide: neurological and haematological toxic effects, especially with prolonged use

**Keywords:** Nitrous oxide, neurological, haematological toxicity

Neurological and haematological toxic effects can occur with prolonged use of nitrous oxide. Neurological effects can occur without preceding overt haematological changes. Assessment of vitamin B12 levels should be considered before nitrous oxide anaesthesia in people with risk factors for deficiency

Nitrous oxide is a medical gas used very widely in surgical anaesthesia. As a 50% mixture with oxygen (brands include Entonox), it is also widely used to relieve pain in childbirth and in acute trauma.

### Risk with prolonged use

Nitrous oxide has a very good safety profile in normal use under the supervision of a healthcare professional. However, prolonged use may lead in rare cases to megaloblastic anaemia and neurological toxic effects (myelopathy) due to inactivation of vitamin B12.

For this reason, nitrous oxide should not be given continuously for more than 24 hours, or more frequently than every 4 days, without close clinical supervision and haematological monitoring.

Neurological toxic effects can occur without anaemia or macrocytosis, and even when B12 levels are in the normal range.

### Vitamin B12 deficiency

In patients with subclinical deficiency of vitamin B12, neurological toxic effects have occurred after a single exposure to nitrous oxide during general anaesthesia. Assessment of vitamin B12 levels should be considered before nitrous oxide anaesthesia in patients with risk factors for deficiency of this vitamin. Individuals at risk include elderly people, those who have a poor or vegetarian diet, and those with a history of anaemia.

Nitrous oxide is a licensed medicinal product. Updated Summaries of Product Characteristics will be available in due course.

**Advice for healthcare professionals:**

- Neurological and haematological toxic effects can occur with prolonged use of nitrous oxide. For this reason, nitrous oxide should not be given continuously for more than 24 hours, or more frequently than every 4 days, without close clinical supervision and haematological monitoring
- Neurological toxic effects can occur without preceding overt haematological changes
- Assessment of vitamin B12 levels should be considered before nitrous oxide anaesthesia in people with risk factors for deficiency of this vitamin. Specialist haematological advice should be sought as appropriate

# Rituximab and efalizumab: progressive multifocal leukoencephalopathy

**Keywords:** rituximab, MabThera, efalizumab, Raptiva, progressive multifocal leukoencephalopathy, PML, non-Hodgkin's lymphoma, rheumatoid arthritis, plaque psoriasis

Progressive multifocal leukoencephalopathy (PML) has been reported in association with the use of some monoclonal antibodies. Patients should be monitored regularly for neurological symptoms or signs that might suggest PML. If PML is suspected, treatment must be suspended until PML has been excluded

## Progressive multifocal leukoencephalopathy: association with some monoclonal antibodies

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disorder of the CNS, which presents with rapidly progressive focal neurological deficits including hemiparesis, paraesthesiae, visual-field deficits, ataxia, and cognitive and behavioural changes. The outcome is usually rapidly fatal. PML is caused by reactivation of the JC virus—a human polyomavirus, which is latent in 70–90% of adults. PML occurs almost exclusively in immunocompromised patients and has been reported in association with the use of some monoclonal antibodies including natalizumab (Tysabri▼, a treatment for multiple sclerosis) and rituximab (MabThera).

For drug safety advice for natalizumab see Drug Safety Update September 2008, p 7; www.mhra.gsi.gov.uk/mhra/drugsafetyupdate

## Rituximab: first report of PML in rheumatoid arthritis indication

Rituximab is indicated in combination with methotrexate for adults with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying antirheumatic drugs including one or more tumour necrosis factor inhibitors. Rituximab is also indicated for the treatment of follicular non-Hodgkin's lymphoma and diffuse large B cell non-Hodgkin's lymphoma.

76 cases of confirmed or suspected PML have been reported in patients treated with rituximab, mainly when used in oncological indications. In June 2008, the first report of PML in a patient with rheumatoid arthritis treated with rituximab was received. PML was diagnosed 18 months after the last dose of rituximab; the patient had also been exposed to chemotherapy for oropharyngeal cancer, which could have been relevant in this case.

## Efalizumab: first reports of PML

Efalizumab (Raptiva▼) is indicated for the treatment of adults with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant of other systemic therapies including ciclosporin, methotrexate, and PUVA.

See also letters sent to healthcare professionals in November 2008: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm

Reports of two cases of PML were received in September and November 2008, respectively. The patients had been treated with efalizumab for more than 3 years. PML was diagnosed on the basis of clinical symptoms, MRI findings, and detection of JC viral DNA in cerebrospinal fluid. The patients died about 2 months after the onset of neurological symptoms.

**Advice for healthcare professionals:**

- Patients on rituximab or efalizumab should be monitored clinically at regular intervals for neurological symptoms or signs that might suggest PML
- If PML is suspected, treatment must be suspended until PML has been excluded
- If doubt exists, further evaluation including MRI, testing of cerebrospinal fluid for JC viral DNA, and repeat neurological assessment should be considered

Access the Summaries of Product Characteristics at http://emc.medicines.org.uk/

Important information on the use of rituximab and efalizumab can be found in the Summaries of Product Characteristics, which are being updated with this safety information.

## Has your colleague seen this bulletin?

# Yellow Card Scheme update

For drug-safety advice for varenicline see Drug Safety Update November 2008, p2; www.mhra.gov.uk/mhra/drugsafetyupdate

See Drug Safety Update November 2008, p8 for information on rimonabant.

For more information on the HPV vaccination campaign see Drug Safety Update September 2008, p4–5; www.mhra.gov.uk/mhra/drugsafetyupdate

For more information on patient and public reporting see Drug Safety Update February 2008, p 7; read more about the pharmacy promotion in the June 2008 Drug Safety Update, p 6.

More on the enhanced reporting form can be found in the April issue of Drug Safety Update, p 6.

Download DAPs at http://www.mhra.gov.uk/daps; see also Drug Safety Update May 2008, p 6.

## Highlights of 2008

The Yellow Card Scheme continues to be a vital tool for monitoring the safety of medicines in the clinical setting. Some notable achievements have been made in 2008, and we would like to thank those who have sent us reports of suspected adverse drug reactions.

As of Oct 31, 2008, we had received 21 359 reports of suspected adverse drug reactions (ADRs) in 2008, 59% (12 609) of which arrived via the Yellow Card Scheme and and the remainder from pharmaceutical companies. During 2009 we will be looking at ways to increase the number of ADRs sent directly to us via the Yellow Card Scheme.

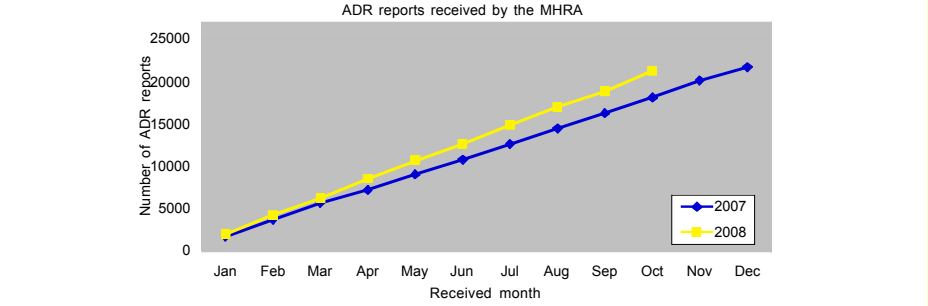
Yellow Cards provide a vital early-warning system that enables us to identify risk factors and give advice on how medicines can be used more safely. For example, data from the Yellow Card Scheme have been an important source of information about the emerging safety profile for the smoking-cessation drug varenicline.

Alongside other data sources, Yellow Cards have also provided supporting evidence for the change in the benefit-risk profile for rimonabant, the marketing authorisation for which was suspended in October 2008.

Moreover, the Yellow Card Scheme continues to play an important part in the surveillance of the safety of human papillomavirus vaccine after the launch of the national immunisation campaign in September this year.

### 2008: an important year for the Yellow Card Scheme

- In February 2008, patients and the general public were welcomed as established reporters to the Scheme. To supplement reporting by the general public, a 6-week promotional campaign took place in community pharmacies
- In February, we also launched an updated online Yellow Card at www.yellowcard.gov.uk—a simple, fast, and paper-free way to report suspected adverse drug reactions
- Drug Analysis Prints—anonymised online listings of suspected adverse drug reactions reported to us—are available on our website. They are now updated monthly, giving a useful overview of the reporting patterns for a particular medicine




You can keep up to date with the latest news about the Yellow Card Scheme in 2009 through regular updates in Drug Safety Update.

Please continue to send us Yellow Cards of suspected adverse drug reactions, including suspected drug interactions. The continued success of the Scheme depends on your vigilance and willingness to report. Remember: don't delay, report today!

Quiz

## End-of-year quiz: test your drug-safety knowledge

An answer can be regarded as correct if one part of the whole question is answered correctly. Remember that some articles in Drug Safety Update are more relevant for some healthcare professionals than for others, so feel free to attempt only the questions related to your specialty!

If you participate in Continuing Professional Development/Continuing Medical Education, you may be able to use the completed quiz as evidence of learning through the reading of past issues of Drug Safety Update. To claim personal CPD points in this way, we suggest that you keep a copy of the quiz, together with your answers and the bulletin articles.

**Please do not send your answers to us, this quiz is just for fun!**

**Q1:** Name an important interaction to consider when prescribing **atorvastatin**, and a neuropsychiatric side-effect associated with **statins** as a class.

**Q2:** What important information should be given to patients who are prescribed **varenicline** and their carers, given that suicidal thoughts and behaviour have been reported?

**Q3:** **Rosiglitazone** should not be prescribed for patients with type 2 diabetes with which cardiovascular conditions?

**Q4:** Compared with second-generation pills, is the risk of venous thromboembolism in users of the **Evra contraceptive patch**: a) roughly the same; or b) slightly higher?

**Q5:** Can Dianette (**co-cyprindiol**) be used solely for contraception? After how long on treatment should most women be able to stop using this drug for treatment of acne?

**Q6:** What psychiatric signs and symptoms should those who are prescribed **antiepileptics** watch out for? Which ethnic subgroups should undergo genetic testing before **carbamazepine** prescription?

**Q7:** Which **antianginal** medicine associated with mouth ulcers has more recently been found to be associated with ulceration of any region of the gastrointestinal tract? What is the only effective course of action?

**Q8:** What side-effects should you monitor for in patients on long-term **cabergoline** or **pergolide** for Parkinson's disease? How should you monitor for these effects?

**Q9:** What factors should be taken into account when considering whether to give **epoetins** to patients with anaemia related to cancer chemotherapy?

**Q10:** What local and systemic factors may lead to a potentially dangerous increase in serum **fentanyl** levels (other than dosing error)?

Check your answers on page 10 and in the original Drug Safety Update article at www.mhra.gov.uk/mhra/drugsafetyupdate (citation given at the end of the answer).

# Stop press

## Conventional (typical) antipsychotics: increased mortality in dementia

A European assessment has concluded that conventional (typical) antipsychotics are associated with increased mortality when used in elderly people with dementia. In 2005, analyses of 17 placebo-controlled trials found that atypical antipsychotics were associated with a small increased risk of death in elderly people with dementia (about 1–2% increased risk compared with no treatment). Since then, further data[1,2] have become available that suggest a similar increased risk with conventional antipsychotics, although the underlying mechanism is unknown.

No conclusion can be drawn on whether the risk differs between individual antipsychotics within each class (ie, conventional or atypical). At present, it is reasonable to assume that the increased risk now noted for conventional antipsychotics applies to all drugs in this class.

For further information see: statement from the European Medicines Agency at http://www.emea.europa.eu/pdfs/human/opiniongen/Conventional_Antipsychotics_Article5.3-CHMP_Opinion.pdf, with an accompanying report and question-and-answer document at http://www.emea.europa.eu/pdfs/human/opiniongen/Conventional_%20Antipsychotics_Article5.3-Appendix1-CHMPAR.pdf and http://www.emea.europa.eu/pdfs/human/opiniongen/Conventional_antipsychotics_Article_5.3-Q&A.pdf, respectively

1 Schneeweiss S, et al. *CAMJ* 2007; **176:** 627–32.

2 Gill SS, et al. *Ann Intern Med* 2007; **146:** 775–86.

## Prograf and Advagraf (tacrolimus): serious medication errors

Prograf and Advagraf contain the immunosuppressant **tacrolimus**, but are given according to different dosing schedules.

Medication errors have resulted in patients being dosed incorrectly. This has caused serious adverse reactions, including biopsy-confirmed acute rejection of transplanted organs and toxic effects due to overexposure.

It is important to note the correct use of these medicines:

- Prograf is an immediate-release formulation that must be taken twice a day: once in the morning and once in the evening
- Advagraf is a prolonged-release formulation that must be taken once a day in the morning

Prograf and Advagraf are not interchangeable without careful therapeutic monitoring. Substitution should be made only under close supervision of a transplant specialist.

Particular care should be taken in prescribing and dispensing the correct brand of tacrolimus (ie, Prograf or Advagraf). Prescribers, pharmacists, and patients should be fully aware of the brand being prescribed and the associated dose regimen.

## Norfloxacin: restricted use in urinary infections

The European Medicines Agency has concluded that the oral fluoroquinolone **norfloxacin** (Utinor) should not be used to treat acute or chronic complicated pyelonephritis. The Agency's Committee for Medicinal Products for Human Use concluded that this indication should be withdrawn because efficacy has not been adequately shown for this type of infection, and because the benefits of norfloxacin do not outweigh the potential risks in this indication.

Further information can be found at http://www.emea.europa.eu/pdfs/human/press/pr/38026008en.pdf

**Advice for healthcare professionals:**

- Oral norfloxacin should no longer be prescribed for newly diagnosed complicated pyelonephritis
- Prescribers should review any patient taking oral norfloxacin for complicated pyelonephritis at their next scheduled visit, and should consider the need for alternative treatment if signs or symptoms of infection are persisting

## Hedrin: keep treated hair away from sources of fire

Hedrin contains dimeticone and is used in the treatment of headlice. In 2007, a patient who was using the product set fire to his hair. Although the product itself is not flammable, the labelling was updated to include the following statement:

**"Warning: Hair should be kept away from naked flames, cigarettes and other sources of ignition while treatment with Hedrin is underway. Hedrin is not water based and will not prevent hair from burning"**

Some older stock that does not include this warning in the product labelling may still be circulating in the supply chain. Pharmacists are asked to remind parents and patients who purchase Hedrin to ensure that while treatment is under way hair should be kept away from sources of fire.

## Melanotan: an unlicensed medicine, the risks of which are unknown

Melanotan I and melanotan II are types of peptide hormones that increase the levels of the pigment melanin in the body.

Melanotan is an unlicensed medicine in the UK: its quality, safety, and efficacy have not been established. Melanotan I and melanotan II are allegedly intended for research purposes only. To comply with legislative requirements, the person in charge of the research needs to present a signed order to a pharmacist. The order must state the name of the company, purpose for which the medicine is being used, and quantity needed.

For further information on these legislative requirements see www.opsi.gov.uk

The MHRA is aware that melanotan is being sold on various websites and in some tanning salons and gyms as an injectable product that gives the effect of a 'suntan'. It is against the law to sell or advertise unlicensed medicines in the UK. As at November 2008, the MHRA has contacted 18 companies to explain this legal position and to state that these products must stop selling these products immediately, with cancellation of all advertising.

At present, we do not know how serious any side-effects of melanotan might be. Melanotan has to be reconstituted with water for injection (eg, bacteriostatic water for injections) before subcutaneous administration. Given this route of administration, the risk to public health is potentially high.

**Advice for healthcare professionals:**

- Melanotan is not a licensed medicine—its risks are unknown.
- If you are aware of a patient who has used melanotan and who may have had a side-effect from it, please report the case to us using a Yellow Card (see www.yellowcard.gov.uk)
- Please note you can report anonymously to us any commercial sites (including websites) that sell or advertise melanotan. Call the MHRA's Central Enquiry Point on 020 7084 2000

Further information is available at http://www.mhra.gov.uk/NewsCentre/index.htm

## Tigecycline reformulation affects compatibility: correction

An article about the reformulation of the antibacterial tigecycline in the November 2008 issue of Drug Safety Update (p 4) originally contained statements about the indication of this drug that went beyond the regulatory position. These statements were removed from the article, and an updated version of the article was published on Friday Nov 7.

# Other information from the MHRA

## Patient Information Leaflet of the month: sertraline, Molipaxin, and amisulpiride

Patient information leaflets (PILs) are improving in quality as a result of new legal obligations on manufacturers to test the documents with 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 enable 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. To coincide with the Ask About Medicines Week campaign on mental health, three new leaflets have been added to the site: **sertraline** and **Molipaxin** (trazodone) used to treat depression, and **amisulpiride** used in schizophrenia.

Access these PILs of the month at:
http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleaflets andpackaging/Patientinformationleaflet(PIL) ofthemonth/index.htm'

Ask About Medicines:
http://www.askaboutmedicines.org/

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

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**Report a suspected adverse drug reaction at http://www.yellowcard.gov.uk**

# Quiz answers

**Q1:** Atorvastatin interactions: potent CYP3A4 inhibitors (eg, itraconazole, clarithromycin, HIV protease inhibitors); ciclosporin; verapamil; amiodarone; diltiazem; grapefruit juice; warfarin/coumarins; fibrates; and ezetimibe. Furthermore, inducers of CYP3A4 (eg, efavirenz, rifampicin, and St John's wort) may reduce plasma concentrations of atorvastatin. Neuropsychiatric class effects: sleep disturbances; memory loss; and depression (January issue, p 2 and February issue, p 2). Peripheral neuropathy is another class neurological effect.

**Q2:** Patients should stop treatment and contact their doctor immediately if they develop suicidal thoughts or behaviour: stop varenicline immediately if agitation, depressed mood, or changes in behaviour are observed that are of concern to the patient, family, or caregivers (November issue, p 2).

**Q3:** Rosiglitazone is contraindicated in patients with acute coronary syndrome and in patients with heart failure or history thereof. It is not recommended for patients with ischaemic heart disease or peripheral arterial disease because of an increased risk of myocardial infarction in these patients (February issue, p 9).

**Q4:** Compared with second-generation pills, risk of VTE is thought to be slightly higher in users of the Evra patch (April issue, p 3).

**Q5:** No, Dianette is indicated as a second-line treatment for acne and should not be used solely for contraception because of the increased risk of VTE. Most women who are prescribed Dianette for acne will be able to effectively discontinue treatment 3–4 months after resolution of symptoms (April issue, p 4).

**Q6:** Patients should be alert to any mood changes, distressing thoughts, or feelings about suicide or harming themselves at any point during treatment: antiepileptic treatment is associated with a small increased risk of suicidal thoughts and behaviour (August issue, p 2). Individuals of Han Chinese, Hong Kong Chinese, or Thai origin should be screened for the *HLA-B*1502* allele before prescription of carbamazepine because of a risk of severe skin reactions, particularly Stevens-Johnson syndrome (April issue, p 5).

**Q7:** Nicorandil. Ulcers that may result from nicorandil are refractory to treatment and respond only to drug withdrawal, which should be done only under the supervision of a cardiologist (June issue, p 5).

**Q8:** Patients prescribed cabergoline and pergolide must be monitored for signs of cardiac fibrosis by use of echocardiography before treatment and regularly during treatment (July issue, p 9). It is also appropriate to perform baseline investigations of erythrocyte sedimentation rate or other inflammatory markers, lung function or chest radiography, and renal function before treatment initiation. Fibrotic disorders can have an insidious onset, and patients should be regularly monitored during treatment for possible manifestations of progressive fibrosis.

**Q9:** The decision to give epoetins should be based on an informed assessment of the risks and benefits of treatment, involving the patient. The following should be considered: tumour type and stage; degree of anaemia; life-expectancy; environment in which the patient is being treated; and patient preference (August issue, p 3).

**Q10:** Increased body temperature, exposure to external heat source, concomitant use of CYP3A4 inhibitors (eg, ritonavir, itraconazole, erythromycin, and amiodarone; September issue, p 2).

**How did you score?**

Score 8–10:
Excellent—Drug Safety Update expert

Score 5–7:
Very good

Score below 5:
Stay up to date: keep reading Drug Safety Update!