

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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Welcome to the June issue of *Drug Safety Update*. This month, our Drug Safety advice focuses on two medicines. First, we have a safety overview of a first-in-class treatment for multiple sclerosis. We hope that this safety overview of the monoclonal antibody natalizumab is useful for specialists who may treat patients with this drug (p 2). Second, we would like to remind healthcare professionals about the risk of gastrointestinal or perianal ulceration associated with nicorandil—a widely used treatment for angina. Importantly, these ulcers are refractory to treatment; they respond only to withdrawal of nicorandil (which should be done only under the supervision of a cardiologist). Please read our advice to consider nicorandil as a suspect cause of symptoms of gastrointestinal ulceration (p 5).

This reminder has been issued as a result of a consultant surgeon who emailed us to say that his hospital is seeing patients with this complication from nicorandil treatment. We appreciate all feedback we continue to receive, both about the bulletin and about drug safety. Please remember that you can tell us about any suspected concerns you have about adverse events for a particular medicine by completing a Yellow Card (see www.yellowcard.gov.uk, p 6).

Also this month, our Hot topic summarises current data for ezetimibe, a selective inhibitor of intestinal cholesterol absorption. In April 2008, the results of the ENHANCE trial suggested no benefit from the addition of ezetimibe to simvastatin on the rate of atherosclerosis progression (as measured by carotid intima media thickness) compared with simvastatin plus placebo. The MHRA, together with other regulatory agencies in the European Union, is currently reviewing the results of the ENHANCE trial; read more on p 7.

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.

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Drug safety advice

Natalizumab (Tysabri): safety overview—progressive multifocal leukoencephalopathy, hypersensitivity, and hepatotoxicity

Keywords: natalizumab, Tysabri▼, humanised monoclonal antibody, multiple sclerosis, progressive multifocal leukoencephalopathy, hypersensitivity, infection, hepatotoxicity, melanoma

Patients should be monitored regularly for progressive multifocal leukoencephalopathy (PML) and impaired liver function. If a patient develops PML, natalizumab must be permanently discontinued; patients must be given the alert card that gives information about symptoms of PML. Treatment should also be discontinued for those who have substantial liver injury. In cases of hypersensitivity reactions, treatment should not be resumed if there are persistent (ie, >6 weeks) antibodies to natalizumab after an initial short exposure

Natalizumab (Tysabri ▼) is a recombinant humanised IgG4 monoclonal α 4-integrin antibody indicated for the treatment of 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.

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. Continued treatment must be considered carefully in patients who show no evidence of benefit after 6 months. Data are not available for the safety and efficacy of natalizumab beyond 2 years.

Key safety information

Natalizumab was marketed in the European Union in April 2006. It is estimated that at least 1000 patients in the UK are receiving this drug. 18 UK reports of adverse drug reactions have been received to date, including one report with a fatal outcome. These reports have not, to date, raised any previously unidentified safety issues.

Known safety risks associated with natalizumab that were identified at marketing include progressive multifocal leukoencephalopathy (PML), hypersensitivity reactions, and opportunistic infections.

Further potential risks have since been identified, such as hepatotoxicity and malignant disease including melanoma.

Hepatic reactions

During the postmarketing period 17 spontaneous reports of hepatic adverse events have been received in association with natalizumab in the EU. Signs of liver injury occurred as early as 6 days after the first dose. None of the reported cases led to death or liver transplantation.

Access the European Public Assessment Report for natalizumab at <http://www.emea.europa.eu/humandocs/Humans/EPAR/tysabri/tysabri.htm>

Access the Summary of Product Characteristics for natalizumab at <http://emc.medicines.org.uk/>

Mullen JT, et al. *N Engl J Med* 2008; **358**: 647–48.

Melanoma

There have been two literature reports of melanoma in close temporal relationship with natalizumab. This new risk is currently under review in Europe and further safety studies are being planned.

The following side-effects identified from clinical trial data are listed in the prescribing information:

• Infections and infestations	<i>Common*</i>	Urinary-tract infection Nasopharyngitis
• Immune-system disorders	<i>Common</i> <i>Uncommon</i>	Urticaria Hypersensitivity
• Nervous-system disorders	<i>Common</i>	Headache Dizziness
• Gastrointestinal disorders	<i>Common</i>	Vomiting Nausea
• Musculoskeletal and connective-tissue disorders	<i>Common</i>	Arthralgia
• General disorders and administration-site conditions	<i>Common</i>	Rigors Pyrexia Fatigue

* Incidence in clinical trials more than one in 100 people, but fewer than one in ten.

Has your colleague seen this bulletin?

Advice for healthcare professionals:

Initiation of treatment

- Natalizumab should be initiated and supervised by specialist physicians with experience in the diagnosis and treatment of neurological conditions
- Before initiation of treatment with Tysabri, a recent MRI scan should be available
- Patients treated with natalizumab must be given the special alert card, which gives information about symptoms of PML

Contraindications—the following people should not receive natalizumab

- Those with hypersensitivity to natalizumab or any of its excipients (see Summary of Product Characteristics for excipients)
- Those with PML
- Patients with increased risk of opportunistic infections, including those who are immunocompromised
- Those who are receiving beta-interferon or glatiramer

- Those with known active malignant disease, except patients with cutaneous basal-cell carcinoma
- Children and adolescents

Special warnings for use*PML*

- Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. Natalizumab must be permanently discontinued if a patient develops PML

Hepatic reactions

- Patients should be monitored regularly for impaired liver function. Natalizumab should be discontinued for patients who have substantial liver injury

Hypersensitivity reactions, including anaphylactic or anaphylactoid

- Physicians should counsel patients on the importance of uninterrupted dosing, particularly in the early months of treatment
- Treatment should not be resumed if there are persistent (ie, >6 weeks) antibodies to natalizumab after an initial short exposure

For further information, see section 4.8 of the Summary of Product Characteristics.
<http://emc.medicines.org.uk/>

Reporting of suspected adverse reactions to natalizumab

As with all medicines, the safety of natalizumab remains under close review. Please continue to report to the MHRA and the Commission on Human medicines all suspected adverse reactions to natalizumab via the Yellow Card Scheme.

See
www.yellowcard.gov.uk

Nicorandil: gastrointestinal ulceration

Keywords: nicorandil, Ikorel, angina, ulceration, mouth, gastrointestinal tract, perianal

Nicorandil is associated with a risk of gastrointestinal ulceration, including perianal ulceration. Healthcare professionals should consider nicorandil treatment as a possible cause in patients who present with symptoms of gastrointestinal-tract ulceration

Nicorandil (Ikorel) is widely prescribed for the prevention and treatment of angina. Recommended initial dose is 10 mg twice a day, although 5 mg twice a day can be given (particularly for those who are susceptible to headache). This dose should be titrated up, depending on clinical response: usual dose is 10–20 mg twice a day; up to 30 mg twice a day may be used if necessary.

Although mouth ulceration has long been recognised as a side-effect of nicorandil treatment, its use has more recently been associated with ulceration of any region of the gastrointestinal tract including the perianal area. The ulceration is commonly severe and, in a few patients, has led to perforation. Time to onset may vary widely.

Ulcers that result from nicorandil are refractory to treatment, including surgery; they respond only to withdrawal of nicorandil. However, nicorandil is frequently overlooked as a potential cause for such ulcers,¹ and patients may therefore undergo unnecessary and unsuccessful procedures before the cause is recognised.

¹ Baker RP, et al. *Tech Coloproctol* 2007; **11**: 343–45.

Advice for healthcare professionals:

- GPs and other healthcare professionals should consider nicorandil treatment as a possible cause in patients who present with symptoms of gastrointestinal ulceration
- Ulcers that result from nicorandil are refractory to treatment; they respond only to withdrawal of nicorandil
- Nicorandil withdrawal should take place only under the supervision of a cardiologist

Yellow Card Scheme update

The Yellow Card Scheme collects information on suspected adverse drug reactions (ADRs) in the UK. See www.yellowcard.gov.uk

See BBC News Feb 18, 2008:
<http://news.bbc.co.uk/1/hi/health/7247681.stm>

Pharmaceutical Journal Feb 16, 2008:
http://www.pjonline.com/editorial/20080216/news/news_yellowcard.html

Chemist & Druggist Feb 18, 2008:
<http://www.chemistanddruggist.co.uk/1>

and MHRA press release Feb 18, 2008:
<http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON013940>

See *Drug Safety Update* February 2008 and April 2008:
www.mhra.gov.uk/mhra/drugsafety/update

Please contact yellowcard@mhra.gsi.gov.uk if you would like additional promotional materials or patient Yellow Cards

Promotion of the Scheme in community pharmacies

In February 2008, members of the public were welcomed as established reporters to the Yellow Card Scheme. To support this initiative, a 6-week promotional campaign took place in community pharmacies across the UK. This was combined with several articles in the general and professional press to encourage community pharmacists and members of the public to report any suspected side-effect to any medicine, including over-the-counter products or herbal remedies, using a Yellow Card.

To coincide with the campaign, an updated online reporting form was also launched. Accessible from www.yellowcard.gov.uk, reporting online is a simple, fast, and paper-free way to report ADRs for both healthcare professionals and members of the public.

For the campaign the pharmacies were sent packs that contained promotional materials, including a poster, information cards and guidance notes as well as the newly designed patient-reporting forms. As a result of the increased awareness we received more than 500 reports from members of the public. This number is a marked increase compared with the same period last year when 250 reports were received from the public. Moreover, we have also seen a rise of 20% in reports received online.

Although the official campaign is complete, we continue to encourage all healthcare professionals to talk to their patients about the Yellow Card Scheme, and to report all reactions to new medicines and serious reactions to established medicines. Information about the Yellow Card Scheme is available at www.yellowcard.gov.uk. Through helping to raise the awareness of the Yellow Card Scheme and through increased reporting by all, we can help to continually safeguard public health and to help patients have a better understanding of the medicines they are taking.

It is vital that healthcare professionals continue to report through the Yellow Card Scheme because the clinical details that you provide in your ADR reports are of great importance in the assessment of adverse reactions. We have an automated duplicate-report detection system in place, so please do not be deterred from reporting because you think that the patient (or another healthcare professional) might also report the same suspected ADR.

After the launch of the updated online Yellow Card, feedback has been positive. If you have any comment or ideas for how we can continue to improve the site please email us at: yellowcard@mhra.gsi.gov.uk.

Hot topic

1 Kastelein JJP, et al. *N Engl J Med* 2008; **358**: 1431–43.

For more details on ENHANCE, see the National Prescribing Centre's MeReC Rapid review <http://www.npci.org.uk/blog/?p=97>

The NPC also has e-Learning materials about lipids and cardiovascular disease; see http://www.npci.org.uk/therapeutics/cardio/cdlipids/workshops/workshop_60minute_elearn_event1.php

Ezetimibe: new data from the ENHANCE trial

Ezetimibe selectively inhibits intestinal absorption of cholesterol, primarily lowering low-density lipoprotein (LDL) cholesterol. As monotherapy (brand name Ezetrol ▼), ezetimibe is indicated for patients with high cholesterol in whom a statin is considered inappropriate or is not tolerated. Ezetimibe combined with simvastatin (as the brand name Inegy ▼) is indicated as adjunctive treatment to diet for patients with high cholesterol who do not have appropriately controlled cholesterol with a statin alone.

In April 2008, the ENHANCE¹ trial (Ezetimibe and Simvastatin in Hypercholesterolaemia Enhances Atherosclerosis Regression) suggested no benefit from the addition of ezetimibe to simvastatin on the rate of atherosclerosis progression compared with simvastatin with placebo. ENHANCE was a 2-year clinical trial in 720 patients with familial hypercholesterolaemia—a disorder characterised by high LDL cholesterol and increased risk of premature coronary artery disease. Patients were randomly assigned to simvastatin plus placebo, or to simvastatin plus ezetimibe. The primary endpoint was mean change in intima–media thickness of the carotid artery, as measured by ultrasonography as a surrogate marker for progression of atherosclerosis and risk of cardiovascular adverse events.

The results¹ showed that patients assigned simvastatin plus ezetimibe had significantly lower mean LDL cholesterol than did those assigned simvastatin plus placebo at the end of the study (3.65 mmol/L [SD 1.36] vs 4.98 mmol/L [SD 1.56]; difference between groups 16.5%, $p < 0.01$). However, mean change in intima–media thickness of the carotid artery did not differ significantly between groups (0.0111 mm [SE 0.0038] vs 0.0058 mm [SE 0.0037], respectively, $p = 0.29$).

To date, no data from large clinical outcomes trials are available for ezetimibe. The ongoing IMPROVE-IT trial (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) is evaluating the clinical benefit—in terms of cardiovascular morbidity and mortality—of ezetimibe combined with simvastatin compared with simvastatin alone in about 10 000 patients with acute coronary syndromes. However, the results are not expected to be available in the next 4 years.

The MHRA, together with other regulatory agencies in the European Union, is currently reviewing the results of the ENHANCE trial to establish their clinical significance and potential effect on the balance of benefits and risks for ezetimibe. We will inform healthcare professionals of any changes to prescribing advice as soon as these reviews have been completed.

Stop press

Herbal products marketed for erectile dysfunction

The MHRA has received several warnings from various overseas regulatory authorities about seven products that are being marketed as dietary supplements or “herbal Viagra” for erectile dysfunction (Power 1 Walnut, China Vigour, Herb Vigour, Natural Vigour, VPXL No. 1 Dietary Supplement for Men, Blue Steel, and Hero). All products contain prescription-only medicines such as glibenclamide (an antidiabetic), or sildenafil (or its analogue nor-acetildenafil) or tadalafil (sildenafil and tadalafil are used to treat erectile dysfunction).

Power 1 Walnut (which tested positive for glibenclamide, and sildenafil) was highlighted by the Singapore authorities after the death of a middle-aged man and other serious reports of adverse drug reactions (patients were either found unconscious at home or with severe symptoms of very-low blood sugar). The product was labelled as being manufactured by Guangzhou Xinkauili Limited Company. There are 23 confirmed cases of serious adverse reactions to Power 1 Walnut and 53 suspected cases.

The US Food and Drug Administration has also issued warnings to consumers not to purchase or use Blue Steel or Hero products, which contain undeclared and potent substances similar to sildenafil. The products are promoted as natural dietary supplements and are sold over the internet. The undeclared ingredients in these products may interact with prescription drugs (eg, those for diabetes, high blood pressure, high cholesterol, or heart disease) and can lower blood pressure to dangerous levels.

Please remain vigilant for these products. Anyone with information about the sale or supply of these products should contact the MHRA.

The April issue of *Drug Safety Update* (p 7) summarised our continuing efforts to safeguard public health through the introduction of the Traditional Herbal Registration scheme.

Herbal products registered under this scheme have indications based on traditional use and are suitable for use without medical supervision; herbal medicines with a Marketing Authorisation also continue to be available. Remember that standards between herbal products vary widely: most herbal medicines on the UK market are currently unlicensed. Please continue to report via the Yellow Card Scheme any suspected adverse reactions associated with a herbal product.

To contact us, email info@mhra.gsi.gov.uk; call 020 7084 2000 (weekdays 0900 h to 1700 h); or write to 10-2 Market Towers, 1 Nine Elms Lane, London SW8 5NQ

Access past issues of *Drug Safety Update* at www.mhra.gov.uk/mhra/drugsafety/update

See www.yellowcard.gov.uk

Other information from the MHRA

Patient Information Leaflet of the month

New legal requirements on manufacturers require them to test Patient information leaflets (PILs) with potential patients. User-testing makes sure that the presentation of the information enables patients to find and understand key messages for safe and effective use of the medicine. To promote this new initiative, we are publishing a series of examples of best practice on our website. The latest in the series is the PIL for Epipen, which is used for emergency treatment of life-threatening allergic reactions. This example shows an alternative pamphlet design and includes diagrams to aid the patient in administering the medicine.

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

Safe use of medical lasers and other optical radiation devices

We have produced guidance on the safe use of medical lasers and other optical radiation devices, including light-emitting diodes (LEDs) and intense pulsed light (IPL) systems (ie, intense light or heat sources). The guidance also reviews equipment used alongside this apparatus (eg, optical fibres). Healthcare professionals who purchase, supply, install, use, or maintain medical, dental, and cosmetic lasers, LEDs, and IPL systems may find this guidance useful.

Access the guidance at
<http://www.mhra.gov.uk/Publications/Safetyguidance/DeviceBulletins/CON014775>

Oxygen cylinders and regulators: top tips leaflet

Oxygen cylinders and regulators are used widely and we receive reports of problems such as lack of training on use; misconnection; and damage. We have produced a leaflet to give healthcare professionals reminders and tips on the care and handling of oxygen cylinders and regulators to keep adverse incidents to a minimum.

Read the leaflet at:
<http://www.mhra.gov.uk/Publications/Postersandleaflets/CON014865>

MHRA challenges and priorities: response to public consultation

We have published a summary on the responses we received from our public consultation on the challenges and priorities for the Agency in the next 5 years. Alongside these responses, we have also published our Corporate Plan for 2008–13 and Business Plan for 2008–09.

Access the reports at:
<http://www.mhra.gov.uk/NewsCentre/CON014983>

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

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