

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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We are closely monitoring the safety of varenicline—the newest medicine for smoking cessation. We continue to receive Yellow Card reports of suspected adverse reactions associated with varenicline, the most frequently reported of which are psychiatric disorders. As Christmas and the time for New-Year's resolutions approach, we remind you to highlight to those taking varenicline the possibility of psychiatric adverse effects (p 2).

Remember that you can help us by reporting suspected adverse reactions to varenicline or any other medicine (www.yellowcard.gov.uk). This month, our Yellow Card Scheme update highlights the importance of reports from community pharmacists for OTC medicines (p 6).

Also this month: articles on ezetimibe (p 7), anticholinergics (p 8), and paracetamol (p 9). Alongside data from Yellow Cards, published literature is another important data source for the MHRA. However, it is important to consider all data sources before reaching conclusions and, as these three articles illustrate, publications that attract significant media attention do not always result in new guidance.

The end of this month's bulletin highlights resources that may help during your consultation with patients. We continue to feature exemplar user-tested Patient Information Leaflets. We also have a reminder that the product labelling on herbal medicines can help consumers check whether the products meet assured standards of safety, quality, and patient information (p 10). Finally, you might like to visit a new section of our website about the lifecycle of a medicine, and suggest that interested patients do the same.

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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Drug safety advice

Varenicline: adverse psychiatric reactions, including depression

Keywords: varenicline, Champix, smoking cessation, depression, suicide, suicidal

Psychiatric disorders are the most commonly reported suspected adverse reactions for varenicline in the UK. Depression and suicide-related events have been reported in patients using varenicline who are trying to stop smoking. Patients who are taking varenicline who develop suicidal thoughts or who develop agitation, depressed mood, or changes in behaviour that are of concern for the doctor, patient, family, or caregiver should stop their treatment and contact their doctor immediately

Information about varenicline from the National Prescribing Centre can be found at http://www.npci.org.uk/therapeutics/resp/smoking/room_smoking.php

See Drug Safety Update, July 2008 p 2; www.mhra.gov.uk/mhra/drugsafetyupdate

See www.yellowcard.gov.uk

Download a summary of reported suspected adverse reactions at <http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/Druganalysisprints/index.htm?indexChar=V>; click on "varenicline"

Varenicline (Champix▼) is a non-nicotine aid to smoking cessation and was launched in the UK in December, 2006. It is a partial agonist at the nicotinic $\alpha 4\beta_2$ receptor, and can help to relieve the cravings and nicotine withdrawal symptoms associated with stopping smoking. Up to the end of June 2008, approximately 450 000 people had used varenicline in the UK.

In the July 2008 issue of Drug Safety Update, we gave important advice for healthcare professionals, patients, and carers relating to the risk of suicidal thoughts and behaviour. Since that time, we have received further reports of suspected adverse events associated with varenicline. As the time of year approaches when many people consider giving-up smoking, we would like to remind you of this advice (outlined below), and to ask you to help ensure that patients, their family, or their caregivers are advised accordingly.

Up to 29 Sept, 2008, 3541 reports of suspected adverse reactions have been received for varenicline via the Yellow Card scheme in the UK.

Alongside psychiatric reactions, sleep disorders (including insomnia and abnormal dreams) and gastrointestinal reactions (particularly nausea and vomiting) have been the most commonly reported side-effects.

It is important to note that the suspected reactions are not necessarily caused by the drug and may relate to other factors such as nicotine withdrawal, other illnesses, or other medications taken concurrently by the patient.

Depression and suicide-related events

Stopping smoking—with or without medication—may be associated with various psychiatric symptoms such as depressed mood (rarely including suicidal ideation), irritability, anxiety and frustration, or anger; stopping smoking may also exacerbate an underlying psychiatric condition. However, suicide-related events have been reported in patients taking varenicline who have no known pre-existing psychiatric conditions and in patients who continued to smoke.

The most frequently reported psychiatric disorders are depression or depressed mood, and suicidal ideation.

NICE guidance

The National Institute for Health and Clinical Excellence (NICE) recommends the use of varenicline as an option for smokers who have expressed a desire to quit, and that it should normally be prescribed only as part of a programme of behavioural support.

When deciding which smoking cessation therapies to use and in which order, prescribers should take into account the contraindications and the potential for adverse effects.

Access NICE guidance for varenicline at <http://www.nice.org.uk/Guidance/PH10>

Advice for healthcare professionals:

- Patients and their family or care-givers should be made aware of the possibility that trying to stop smoking might cause symptoms of depression
- Patients who are taking varenicline who develop suicidal thoughts or behaviour should stop their treatment and contact their doctor immediately
- Varenicline should be discontinued immediately if agitation, depressed mood, or changes in behaviour are observed that are of concern for the doctor, patient, family, or caregiver
- Patients with serious psychiatric illness did not participate in the premarketing studies of varenicline, and the safety and efficacy of varenicline in such patients has not been established. Care should be taken when prescribing varenicline to patients who have a history of psychiatric illness

We continue to closely monitor the issue of psychiatric reactions in patients taking varenicline, and wider European review is ongoing. Please continue to report to us via the Yellow Card Scheme all reactions which you suspect may be related to the use of varenicline—including any considered not to be serious and reactions that are well-recognised. You do not have to be certain about causality; if in doubt, please report at www.yellowcard.gov.uk.

Tigecycline: new formulation affects compatibility

Keywords: tigecycline, Tygacil, intra-abdominal infection, skin and soft-tissue infection, compatibility, amphotericin B, diazepam

Reformulated tigecycline is incompatible with amphotericin B, amphotericin B lipid complex, and diazepam. These medicines should not be given simultaneously with the new tigecycline formulation through the same Y-site. Packaging for the new formulation has an orange highlight on the dose strength

Tigecycline (Tygacil▼) is a glycylicycline antibacterial that is used to treat complicated intra-abdominal infection and complicated skin and soft-tissue infection.

The recommended initial dose for adults is 100 mg, followed by 50 mg every 12 hours for 5–14 days. It is infused intravenously over 30–60 min through a dedicated line or through a Y-site.

New formulation affects tigecycline's compatibility with other medicines

Tigecycline has been reformulated to include three excipients: lactose monohydrate; hydrochloric acid; and sodium hydroxide. The addition of these excipients results in a formulation that is more stable in the presence of oxygen.

Since September 2008, all new orders for tigecycline have been supplied with the new formulation. Please use all existing stocks of the original formulation before using the reformulated drug.

There are important differences between the previous formulation and the new formulation that affect safe use of the drug. The **table** shows the known compatibilities and incompatibilities of the new formulation. Incompatible drugs should not be given simultaneously through a Y-site.

See also a letter for healthcare professionals sent September 2008 at <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON028262>

	New formulation
Incompatible with tigecycline through Y-site delivery	Amphotericin B Amphotericin B lipid complex Diazepam
Compatible for simultaneous infusion with tigecycline through Y-site	Dobutamine Dopamine Lidocaine Potassium chloride Ranitidine Lactated Ringer's solution Theophylline Amikacin Gentamicin Haloperidol Morphine Norepinephrine Reformulated Tazocin (active substances piperacillin/tazobactam) Propofol Tobramycin

See Summary of Product Characteristics at <http://emc.medicines.org.uk/>

Product information has been updated to reflect the different compatibility of the new formulation. Packaging and vials for reformulated tigecycline are distinguishable from the original formulation by an orange highlight on the dose strength:



Advice for healthcare professionals:

- Reformulated tigecycline is incompatible with amphotericin B, amphotericin B lipid complex, and diazepam. These medicines **should not be given simultaneously** with the new tigecycline formulation through the same Y-site.
- Tigecycline must not be mixed with other products for which compatibility data are not available
- Use existing stocks of the original formulation of tigecycline before using the reformulated version. Please remember that the original formulation is also incompatible with some medicines

Yellow Card Scheme update

See Drug Safety Update, September 2008, p 9 and <http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON023105> for information about pharmacy availability of azithromycin for chlamydia.

See <http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Legalstatusandreclassification/Reclassification/index.htm> for further information on reclassification of medicines.

See Drug Safety Update, October 2008, p 8 for information about the safety of theophylline.

Reporting by community pharmacists is encouraged for OTCs

Community pharmacists are a key contact for many patients at the point of care because they: give important information during dispensing about safe use of a medicine; are ideally placed to exercise vigilance about the safety of medicines; and may be the first place someone seeks advice in the community if a person has a side-effect from a medicine—particularly if it was obtained from a pharmacy.

We therefore ask that community pharmacists use Yellow Cards to tell us about any suspected side-effects from a medicine—especially those obtained without a doctor's prescription.

Reclassification of medicines from prescription only to pharmacy

Clamelle (azithromycin) is the first oral antibiotic to be made available without prescription. Pharmacists can dispense this medicine to people older than 16 years who have tested positive for chlamydia and have no symptoms, and to their sexual partners. Stocks of Clamelle are expected to reach pharmacies soon.

12.5 mg **diclofenac** can now be supplied by a pharmacy for short-term (no longer than 3 days) pain relief, and 250 mg **naproxen** can be supplied without prescription for primary dysmenorrhoea.

In 2004, 10 mg **simvastatin** was reclassified to pharmacy availability for moderate-risk coronary heart disease.

As with all medicines, the MHRA will continue to monitor closely the safety of those that have been recently reclassified, and community pharmacists can help. Last month in Drug Safety Update, we asked for the help of community pharmacists in trying to ensure that theophylline is supplied appropriately.

Please report suspected adverse drug reactions to us online

- Please use the Yellow Card Scheme to tell us about suspected adverse drug reactions you have encountered in practice
- You can send Yellow Cards by post, but we strongly recommend reporting online at www.yellowcard.gov.uk. You can submit several reports at once online, and by registering you can keep a log of all your reports
- Reporting online is a natural extension of the daily use of web resources by healthcare professionals, and of the use of electronic resources in patient management

Between September 2007 and August 2008, pharmacists provided an important contribution to the Yellow Card Scheme: 677 reports were received from community pharmacists, 1568 from hospital pharmacists, and 1124 from pharmacists whose speciality was not recorded.

These reports of suspected adverse drug reactions are vital to helping us safeguard public health. If you suspect an adverse drug reaction from a medicine, or combination of medicines, don't delay report today.

Hot topic

No conclusions about the possible effect of ezetimibe on cancer can be drawn from the current data; further assessment will be done when final results of two large ongoing randomised trials become available

Ezetimibe and results of SEAS study: possible increased risk of cancer

Ezetimibe inhibits the absorption of cholesterol from the small intestine. As monotherapy (brand name Ezetrol▼) ezetimibe is indicated for patients with high cholesterol where a statin is considered inappropriate or is not tolerated. Ezetimibe is also available as a combination product with simvastatin (brand name Inegy▼) for patients whose cholesterol is not controlled with a statin alone.

SEAS study

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study¹ compared simvastatin and ezetimibe with placebo to determine whether intensive lipid-lowering improved clinical outcomes in 1873 patients with mild to moderate asymptomatic aortic stenosis. Patients were followed up for an average of 4.35 years.

Treatment with simvastatin and ezetimibe had no effect on the primary endpoint of major cardiovascular events (hazard ratio [HR] 0.96 [95% CI 0.83–1.12]), despite reducing serum LDL-cholesterol levels by approximately 50%. Overall mortality did not differ between the two treatment groups.

An unexpected increase in cancer incidence and mortality was observed in the active treatment arm. Newly incident cancers (of mixed origin) were recorded for 101 (10.7%) patients in the treated group versus 65 (7%) patients in the placebo group (HR 1.55 [1.13–2.12], $p=0.01$). Deaths from cancer were more frequent in the treated group compared with placebo: 39 patients (4.1%) vs 23 patients (2.5%), respectively (HR 1.67 [1.00–2.79], $p=0.05$). However, the SEAS study is limited by its relatively small size and short duration, and it was not powered to detect comparatively infrequent and long-term side-effects.

There is no good evidence that statins increase the risk of cancer,² and so the findings of the SEAS study cast suspicion on ezetimibe rather than on simvastatin.

Meta-analysis of SHARP and IMPROVE-IT trials

To further investigate a possible association, the results of two much larger ongoing trials of ezetimibe have been meta-analysed³: the Study of Heart and Renal Protection (SHARP; $n=9264$, average follow-up 2.7 years) and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT; $n=11353$, average follow-up 1 year). Together these trials provide about four-times more information on cancer incidence than does the SEAS trial and more than four-times the number of patient-years of follow-up.

In this meta-analysis, no excess cancer incidence was observed in groups given ezetimibe. Furthermore, there was no clustering of cancer site; the specific sites most affected in the SEAS study were not similarly affected in the SHARP and IMPROVE-IT studies; and no increase in relative risk was noted with increasing follow-up. The authors conclude that there is no credible evidence for an adverse effect of ezetimibe on cancer.

Advice for healthcare professionals:

The available data have been considered by the Commission on Human Medicines' Pharmacovigilance Expert Advisory Group. They have advised that the data currently available are insufficient to draw any conclusions about the effect of ezetimibe on cancer. Further assessment of this issue will be necessary when the final results of the two large ongoing trials become available.

- 1 Rossebo AB, et al. *N Engl J Med* 2008; **359**: 1343–56.
- 2 Baigent C. *Lancet* 2005; **366**: 1267–78.
- 3 Peto R, et al. *N Engl J Med* 2008; **359**: 1357–66.

Stop press

Rimonabant: European suspension of marketing authorisation

The European Medicines Agency has completed a review of rimonabant (Acomplia, a treatment for obesity) after concerns about its psychiatric safety. The review has concluded that, on the basis of currently available data, the benefits of rimonabant do not outweigh the risks of psychiatric reactions in clinical use. The marketing Authorisation for this medicine has been suspended across the European Union.

Advice for healthcare professionals:

- Prescribers should not issue any prescriptions for rimonabant, and should review the treatment of those who are currently taking this medicine
- Patients who are currently taking rimonabant should consult their doctor or pharmacist at a convenient time to discuss their treatment. If patients wish to stop taking rimonabant, it is safe to do so at any time
- Patients who are currently enrolled in clinical trials of rimonabant may wish to contact the trial investigator (the doctor who is treating them), who will be able to give more information. Trial investigators are being notified of this suspension of the marketing authorisation

See further information on our website at www.mhra.gov.uk and on the European Medicines Agency website at www.emea.europa.eu. A message to healthcare professionals has also been sent through the Central Alerting System—see <https://www.cas.dh.gov.uk>.

Inhaled anticholinergics: recent published data on risk of death or stroke

Tiotropium (Spiriva) and ipratropium (Atrovent) are muscarinic receptor antagonists, which are licensed for the treatment of symptoms of chronic obstructive pulmonary disease (COPD).

Some recently published studies have suggested that inhaled anticholinergics might be associated with an increased risk of cardiovascular death, myocardial infarction, or stroke,¹ and that ipratropium might be associated with an increased risk of cardiovascular death and all-cause mortality,² compared with no treatment or with other treatments for COPD. However, there were limitations in the methods of these studies. Furthermore, a 4-year placebo-controlled randomised double-blind trial of 5993 patients with COPD (the UPLIFT study³) concluded that tiotropium was associated with a non-significantly decreased risk of all-cause mortality, myocardial infarction, or stroke compared with placebo.

These conflicting findings currently make it difficult to draw firm conclusions on the risk of all-cause mortality, cardiovascular death, or stroke associated with inhaled anticholinergics. Further analyses are needed to shed light on any possible increased risk.

Patients with COPD who use tiotropium should be reminded not to exceed the recommended once-daily dose of one Spiriva 18 µg capsule or once-daily dose of two puffs of Spiriva Respimat ▼ 2.5 µg.

- 1 Singh S, et al. *JAMA* 2008; **300**: 1439–50.
- 2 Lee TA, et al. *Ann Intern Med* 2008; **149**: 380–90.
- 3 Tashkin DP, et al. *N Engl J Med* 2008; **359**: 1543–54.

Information from the National Prescribing Centre on this topic can be found at <http://www.npci.org.uk/blog/?p=205> and <http://www.npci.org.uk/blog/?p=223>

Stop press

Paracetamol use in infancy: no strong evidence for asthma link

1 Beasley R, et al, for the ISAAC Phase Three Study Group. *Lancet* 2008; **372**: 1039–48.

A study recently published in *The Lancet*¹ provided results from part of an international collaborative research effort known as “Asthma and Allergies in Childhood”. The study explored the link between paracetamol use in infancy and the risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years. Questionnaire data for more than 200 000 children were obtained from 31 countries worldwide. The results suggested an association between asthma and paracetamol use in the first year of life or use during the previous 12 months, or both.

The study was reviewed by the Commission on Human Medicines’ Pharmacovigilance Expert Advisory Group in October 2008. Because of concerns over data interpretation, the Group advised that the study does not provide strong evidence that paracetamol use in infancy can cause asthma.

Concerns over data interpretation included:

- the possibility that use of paracetamol in infancy reflects treatment of a true underlying cause of asthma such as a viral illness, which necessitated the administration of an antipyretic
- the fact that paracetamol was the only available analgesic in many regions of the world so that the study comparison is between use of analgesics in infancy or not, rather than between the use of paracetamol or not
- the fact that no consideration was given to the effect of parental choice of analgesic, which may be based on the parents’ own asthmatic status and their consequent avoidance of a non-steroidal anti-inflammatory drug

Advice for healthcare professionals, parents, and carers:

The results of this new study do not necessitate any change to the current guidance for use in children. Paracetamol remains a safe and appropriate choice of analgesic in children. There is insufficient evidence from this research to change guidance regarding the use of antipyretics in children.

See also information from the National Prescribing Centre at <http://www.npci.org.uk/blog/?p=206>

Other information from the MHRA

Patient Information Leaflet of the month: Telfast

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. The latest in the series is for **Telfast** (fexofenadine), which is indicated for seasonal allergic rhinitis and chronic idiopathic urticaria.

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)

'My medicine': new section on MHRA website

We have launched a new section on our website that explains how medicines are developed—from laboratory discovery, through trial development, and to licensing and safety monitoring of marketed medicines. We hope that you and your patients find these webpages a useful resource.

'My medicine: from laboratory to pharmacy shelf' can be accessed at <http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Adviceandinformationforconsumers/Mymedicine/index.htm>

Device bulletin: use of in vitro diagnostic devices with other medical equipment

In vitro diagnostic devices are commonly used alongside other medical equipment. Examples include use of point-of-care glucose meters or strips with lancing devices, and reagent kits and automated laboratory analysers. Their use needs careful planning and management to ensure the performance of individual devices or equipment is not impaired.

Read our device bulletin on this topic, which outlines some actions to consider when verifying whether a particular combination will not impair product performance.

Access the bulletin at <http://www.mhra.gov.uk/Publications/Safetyguidance/DeviceBulletins/CON025728>

Herbal medicines: packaging shows MHRA approval

Any herbal product that is approved by the MHRA will have a product licence (PL) number or Traditional Herbal Registration (THR) number on its packaging. Products labelled in this way meet assured standards of safety, quality, and patient information.

We have been made aware of several cases where a product sold as "Goldenroot Complex" (promoted as a herbal alternative to Viagra for erectile dysfunction) has been incorrectly advertised on the internet as regulated and approved by the MHRA. There are no products that contain Golden Root (*Rhodiola rosea*) in the UK that are licensed or registered for erectile dysfunction.

For further information about herbal medicines, see the April 2008 Hot topic of Drug Safety Update, p 7 www.mhra.gov.uk/mhra/drugsafetyupdate

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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