

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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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.

To follow on from advice in our January issue, this month we have further information about statins to help ensure their safe use. Our lead Drug safety advice article this month summarises the potential adverse effects of sleep disturbance, memory loss, sexual dysfunction, depression, and interstitial lung disease associated with statins as a class (page 2).

Also this month, we have further advice on the evolving safety profile for varenicline—a new aid to smoking cessation. Turn to page 3 for the latest information about reported reactions of depression and suicidal ideation in association with varenicline use. Reports can be made online at www.yellowcard.gov.uk

Indeed, the Yellow Card scheme welcomes patients and the public as reporters to the scheme. Until now, patients and the public were able to report to the scheme under a nationwide pilot. Look out for information to promote the scheme to the public in community pharmacies this month.

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Drug safety advice

Statins: class effects identified

Keywords: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, statins, sleep disturbance, insomnia, nightmares, memory loss, sexual dysfunction, depression, interstitial lung disease, class effects

Several additional side-effects—sleep disturbances, memory loss, sexual dysfunction, depression, and interstitial lung disease—have been recognised with statins. The product information for the class as a whole is being updated

Statins (HMG-CoA reductase inhibitors) are used in patients with hypercholesterolaemia and for the prevention of cardiovascular events.

The benefits of statins are well established and outweigh the risk of side-effects in the majority of patients.

Following a review of clinical trial data, spontaneous reports of suspected adverse drug reactions, and published literature, product information for statins is being updated to reflect a number of different side-effects as class effects of all statins.

New advice for healthcare professionals

- Patients should be made aware that treatment with any statin may sometimes be associated with depression, sleep disturbances, memory loss, and sexual dysfunction
- Statins may very rarely be associated with interstitial lung disease. Patients should seek help from their doctor if they develop presenting features of interstitial lung disease such as dyspnoea, non-productive cough, and deterioration in general health (eg, fatigue, weight loss, and fever)

Reporting of adverse events

Healthcare professionals and patients are encouraged to report any suspected adverse drug reactions with statin treatment to us via the Yellow Card scheme.

Previous advice for statins was given in the January 2008 issue of this bulletin: see *Drug Safety Update* 2008; **1**(6): 2–4. See www.mhra.gov.uk/mhra/drugsafety/update

See <http://www.yellowcard.gov.uk/> For news about patient reporting to the scheme, see page 7. Information for atorvastatin (Crestor) has also featured as our Patient Information Leaflet of the month—see *Drug Safety Update* 2008; **1**(6): 10 for further details. See www.mhra.gov.uk/mhra/drugsafety/update

Varenicline: safety update

Keywords: varenicline, Champix, smoking cessation, depression, suicidal thoughts, suicidal behaviour

Depression has been reported in patients using varenicline who are trying to stop smoking, and symptoms of depression may include suicidal thoughts and behaviour. Patients who are taking varenicline who develop suicidal thoughts should stop their treatment and contact their doctor immediately

Has your colleague seen this bulletin?

Varenicline (Champix▼) is a non-nicotine aid to smoking cessation that is authorised throughout Europe. It can help to relieve the cravings and withdrawal symptoms associated with stopping smoking.

The recommended dose of varenicline is 1 mg twice daily after a 1-week titration (titration schedule: 0.5 mg daily for the first three days [days 1–3], then 0.5 mg twice daily for the next three days [days 4–7], increasing to 1 mg twice daily thereafter [day 8 onwards]). However, patients who cannot tolerate the adverse effects of varenicline may receive a lower dose, temporarily or for the full course, of 0.5 mg twice daily.

Champix was first marketed in the UK in December 2006 and since that time the MHRA in conjunction with the European Medicines Agency (EMA) has monitored its safety.

Up to Dec 14, 2007, 1241 reports of *suspected* adverse reactions have been received via the Yellow Card scheme in the UK. The **table** shows reactions most commonly reported through the scheme. 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 medicines taken concurrently by the patient.

Reported reaction	Number of reports	Reported reaction	Number of reports
Nausea	327	Somnolence	40
Headache	125	Suicidal ideation	36
Vomiting	119	Diarrhoea	35
Dizziness	77	Nightmare	35
Abdominal pain	69	Dyspnoea	34
Depression	86	Depressed mood	33
Abnormal dreams	72	Chest pain	31
Insomnia	63	Arthralgia	31
Fatigue	57	Increased sweating	31
Malaise	51	Anxiety	30
Rash	40	Pruritus	30
Sleep disorder	40		

Note: many reports contain more than one of the above reactions. Therefore the sum of the number of reports in this table may exceed the total number of reports.

For further information, access the European Public Assessment Report of varenicline at <http://www.emea.europa.eu/humandocs/Humans/EPAR/champix/champix.htm>

The most commonly reported adverse effects seen during the initial clinical trials of varenicline were nausea (2.7% vs 0.6% for placebo), headache (0.6% vs 1.0% for placebo), insomnia (1.3% vs 1.2% for placebo), and abnormal dreams (0.2% vs 0.2% for placebo).

Risk of depression, including suicidal ideation

Recently, concerns have arisen about reports of suicidal thoughts and behaviour reported in association with the use of varenicline, and these data have been subject to Europe-wide review. After the most recent consideration of available data, product information for doctors and patients is being updated to contain warnings that depression has been reported in patients using varenicline who are trying to stop smoking, and that symptoms of depression may include suicidal thoughts and behaviour.

Combination with other smoking-cessation therapies

The safety and efficacy of varenicline in combination with other smoking-cessation therapies have not been studied. In a short-term (12-day) study of varenicline use with transdermal nicotine-replacement therapy, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was higher for the combination than for nicotine-replacement therapy alone.

Prescribing advice:

- Smoking cessation, with or without pharmacotherapy, may be associated with an exacerbation of underlying psychiatric illness, including depression. Care should be taken in such patients, who should be advised of this risk
- Patients 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 should stop their treatment and contact their doctor immediately

Reporting of suspected adverse reactions to varenicline

As with all new drugs, the safety of varenicline remains under close review. Please continue to report all suspected adverse reactions to the MHRA and the Commission on Human Medicines via the Yellow Card scheme (see www.yellowcard.gov.uk).

Carisoprodol and meprobamate: risks outweigh benefits

Keywords: carisoprodol, meprobamate, abuse, addiction, intoxication, psychomotor impairment, risks and benefits

The Marketing Authorisation for carisoprodol is to be suspended after a European review concluded that the risks of treatment outweigh the benefits. Carisoprodol is associated with increased risk of abuse, addiction, intoxication, and psychomotor impairment. There are safer alternatives to carisoprodol for the management of acute musculoskeletal disorders. A phased withdrawal of carisoprodol from the UK market will take place.

Meprobamate is closely related to carisoprodol and has a similar balance of risks and benefits. The MHRA is therefore exploring a phased withdrawal of this medicine in the UK

Carisoprodol

Carisoprodol (Carisoma) is a centrally acting muscle relaxant used in the short term as an adjunct to the symptomatic treatment of acute musculoskeletal disorders associated with painful muscle spasm.

In the January 2008 issue of Drug Safety Update, a Stop press article (page 10) announced the recent European review of carisoprodol for which the Committee for Medicinal Products for Human Use (CHMP) concluded that the risks of treatment outweigh the benefits. This review was triggered by concerns from the Norwegian Medical Agency that carisoprodol was associated with increased risk of abuse, addiction, intoxication, and psychomotor impairment.

The CHMP has recommended that all Marketing Authorisations for carisoprodol-containing products should be suspended throughout the European Union. It is anticipated that a decision by the European Commission to ratify the CHMP decision will follow in the near future. A key feature of the CHMP opinion is that there are safer alternatives to carisoprodol for the management of acute musculoskeletal disorders where a muscle relaxant is required; one such alternative is a benzodiazepine.

Evidence suggests that carisoprodol can be associated with a withdrawal syndrome.¹ Clinical features include anxiety, insomnia, muscle twitching, and hallucinations, and are thought to be due to withdrawal of meprobamate—the main active metabolite of carisoprodol. When a patient may be physically dependent on carisoprodol, a gradual decrease in dose is required (which might take several weeks for those on high doses). If a withdrawal syndrome occurs, benzodiazepines are recommended in the short term; antipsychotics and antidepressants have also been used.

The MHRA is working with the UK Marketing Authorisation Holder (Forest Laboratories UK Ltd) to achieve a planned withdrawal of carisoprodol from the UK market. The European Commission's decision may be issued before complete withdrawal of carisoprodol in the UK (particularly because there are patients who are physically dependent on the medicine). In these circumstances, essential supply will be possible on a named patient basis.

See
www.mhra.gov.uk/mhra/drugsafety/update

¹ Reeves RR, et al.
Pharmacotherapy 2007; **27**:
1462–66.

Advice for healthcare professionals:

- The UK Marketing Authorisation for carisoprodol is to be suspended
- Treatment with carisoprodol should not be started
- Carisoprodol is associated with a withdrawal syndrome
- When a patient may be physically dependent on carisoprodol, a gradual decrease in dose is required (which might take several weeks for those on high doses)
- Carisoprodol should not be stopped suddenly
- If a withdrawal syndrome occurs, benzodiazepines are recommended in the short term; antipsychotics and antidepressants have also been used

Meprobamate

Meprobamate is a carbamate used for short-term treatment of anxiety states or musculoskeletal disorders where, in either case, there is muscle tension or painful muscle spasm.

Meprobamate shares many of the risks associated with barbiturates, including dependence and withdrawal, and has therefore been mainly superseded by relatively safer medicines. Meprobamate is the main active metabolite of carisoprodol, and the conclusions of the recent European review of carisoprodol are pertinent to meprobamate.

Considering that: there are safer alternative medicines to meprobamate on the market; there are risks of dependence, withdrawal, abuse, and other undesirable effects associated with meprobamate; and the outcome of the European review of carisoprodol is negative, the balance of benefits and risks for meprobamate-containing products is no longer favourable.

The MHRA is in discussion with the three UK Marketing Authorisation Holders for meprobamate-containing products about a phased withdrawal from the UK market. Further details will be provided in due course.

Advice for healthcare professionals:

- Treatment with meprobamate should not be started
- Further information about this medicine will be provided in due course

For full information about meprobamate see Martindale: The Complete Drug Reference, available online at <http://www.medicinescomplete.com/mc/>

Yellow Card scheme update

The Yellow Card scheme collects information on suspected adverse drug reactions. See www.yellowcard.gov.uk

See *Pharmacoepidemiol Drug Saf* 2006; **15** (suppl 1): S105

Reporting by patients and the public

Healthcare professionals continue to provide most (>90%) reports of suspected adverse drug reactions sent in on Yellow Cards. Patients and the public have been able to report since 2005—until now, this has been under a nationwide pilot scheme.

The pilot has been successful—more than 6000 reports of a generally high standard of quality have been received. From February 2008, patients and members of the public will be included as established reporters under the scheme, which will be promoted in community pharmacies across the UK during February 2008.

We are particularly interested in hearing from patients who have had serious reactions or side-effects, or those that are not listed in the product information.

Have you considered talking to your patients about reporting suspected adverse reactions to the Yellow Card Scheme?

Common concerns about patient reporting include the possibility of the system being overwhelmed by large numbers of reports of relatively minor reactions. Our experience is that this is not the case. In an early evaluation of patient reports, we found that serious reactions accounted for a similar proportion of the reports submitted by patients and healthcare professionals.

Although we found that healthcare professionals provided more complete reports, patients gave more information on the effect of the adverse reaction on their quality of life. This finding highlights the important role of patients in reporting to the Yellow Card scheme, supplementing valuable clinical details provided by healthcare professionals with insight into the effect of side-effects on everyday life.

We ask healthcare professionals to continue to report all reactions to new black triangle (▼) medicines, and serious reactions to older established medicines. Furthermore, we encourage all healthcare professionals to talk to patients about the Yellow Card scheme, both to tell a patient that you intend to report (or have reported) via a Yellow Card a side-effect they experienced, and to let them know that they can report should they wish. Information for patients about the Yellow Card Scheme is available at www.yellowcard.gov.uk; this information might also help you to talk to patients about the scheme.

Please do not be deterred from reporting because you think that the patient (or another healthcare professional) might also report the suspected adverse drug reaction: we can identify duplicate reports, and combining them may provide complementary information and a fuller picture about an adverse drug reaction.

Hot topic

Biosimilar products

What is a biosimilar?

A similar biological medicinal product (biosimilar) is a new biological product that has been developed to be similar to an existing biological product (“reference” product).

Biological products are fundamentally different from standard chemical products in terms of their complexity, and it is unlikely that the biosimilar product will have an identical structure to that of the “reference” product, thereby requiring evidence of safety and efficacy before approval. In this regard, biosimilars are different to the more familiar generic products. Examples of biosimilar products include:

Reference product (substance)	Biosimilar products
Genotropin (somatropin),	Valtropin, Omnitrope
Eprex (epoetin alpha)	Binocrit (epoetin alpha)
Eprex (epoetin alpha)	Retacrit (epoetin zeta)

Prescribing of biosimilars

All biosimilar products are prescription only medicines (POM). When prescribing biological products, it is good practice to use the brand name. This will ensure that automatic substitution of a biosimilar product does not occur when the medicine is dispensed by the pharmacist. Products (biosimilar and reference) that have the same international non-proprietary name (INN) are not to be presumed identical for the reasons given above.

Reporting suspected ADRs for biosimilars

In view of the subtle differences that are likely to exist between biosimilar products, even though the clinical effect of the products may be similar, and in view of the complexity of these molecules, it is very important that adverse drug reactions (ADRs) are properly assigned to the suspect product. Particular care needs to be taken when reporting ADRs associated with biosimilar products.

To ensure that any ADR that you report is assigned to the correct product, it is important that the product name rather than the substance name is used for reporting. For example, if reporting an ADR to Eprex, please report using the name Eprex rather than epoetin alpha.

Further information about biosimilar products can be found on the website of the European Medicines Agency.

For guidelines, see
<http://www.emea.europa.eu/htms/human/humanguidelines/multidiscipline.htm>

For questions and answers, see
<http://www.emea.europa.eu/pdfs/human/pcwp/7456206en.pdf>

Stop press

Duphaston/Duphaston HRT (dydrogesterone): withdrawal of Marketing Authorisation

The Marketing Authorisation Holder for Duphaston (dydrogesterone), Solvay Healthcare Ltd, is withdrawing this medicine from the market from March 2008. Duphaston was licensed for use in several indications, including threatened or recurrent miscarriage, dysfunctional uterine bleeding, and hormone-replacement therapy. This medicine is being withdrawn for commercial reasons.

A Public Assessment Report that summarises evidence for the efficacy of progesterone and dydrogesterone in the maintenance of pregnancy is available on our website.

To access the Public Assessment Report, click <http://www.mhra.gov.uk/mhra/safety/warningsandmessagesformedicines>

Herbal safety news: OSAS (intensive body lotion with aloe vera) found to contain steroids

The MHRA has recently found that samples of OSAS (intensive body lotion with aloe vera), an unlicensed product, have tested positive for variable amounts of the corticosteroid betamethasone.

Corticosteroids are used to treat inflammatory skin conditions, especially eczema and psoriasis. Long-term use can cause skin thinning and can worsen conditions such as eczema and dermatitis.

OSAS lotions have been supplied over the internet and from various Asian and African beauty shops for the treatment of eczema and psoriasis.

The lotion was brought to the attention of the MHRA by a paediatric dermatologist, who became concerned when the parent of a baby he was treating for eczema started to use this product on the infant.

We strongly advise that anyone who is using this product, particularly on young children and babies, should stop immediately. Discontinuation of the product may cause a rebound effect (ie, worsening of the condition) and patients should therefore consult a healthcare provider about alternative treatments.

Rosiglitazone: new contraindications and warnings

The European Committee for Medicinal Products for Human Use has recommended new contraindications and warnings for rosiglitazone (Avandia, Avandamet ▼)—a treatment for type 2 diabetes.

Rosiglitazone is now contraindicated in patients with acute coronary syndrome; rosiglitazone has not been studied in controlled trials in this group of patients.

Furthermore, rosiglitazone is not recommended for use in patients with ischaemic heart disease or peripheral arterial disease, because of concerns about an increased risk of myocardial infarction in these patients.

This European assessment has concluded that the benefits of rosiglitazone treatment outweigh the risks in their approved indications, but that the prescribing information should be updated.

For further information, see <http://www.emea.europa.eu>. Drug safety advice for rosiglitazone was included in the December 2007 issue of Drug Safety Update, p 5—<http://www.mhra.gov.uk/mhra/drugsafetyupdate>

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 this series is the PIL for Creon (pancreatin, a high-strength pancreatic-enzyme supplement).

Access PIL of the month at:
http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&nodId=1170

Please report suspected counterfeit medicines

The MHRA has launched a dedicated 24-hour hotline for the reporting of suspected counterfeit medicines and devices. Call 020 7084 2701 or email counterfeit@mhra.gsi.gov.uk if you think you have been offered fake products or think you may have seen or bought such products. We have also recently published our first anti-counterfeiting strategy, which outlines the MHRA's approach to combating the availability of fake medicines and medical devices in the UK for the next 3 years.

Alternatively, you can write to:
Counterfeits, The Intelligence Unit, MHRA,
Market Towers, 1 Nine Elms Lane,
London SW8 5NQ

To access further information about counterfeit products and the Agency's 3-year strategy to combat the issue, see http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&nodId=252

Midwife prescribing: public consultation

The MHRA has launched a public consultation to seek views on proposals to amend the range of medicines that can be sold, supplied, or given by registered midwives in the UK. The proposals intend to benefit patient care by enhancing the ability of midwives to provide safe and effective holistic care for women during childbirth. The consultation period ends on Feb 29, 2008.

To reply to the consultation by Feb 29, 2008, see http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2033207&ssTargetNodId=373

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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