

Drug Safety Update



Latest advice for medicines users

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

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This July issue marks the final issue for volume 1 of *Drug Safety Update*. Since the launch of the bulletin in August 2007, we have aimed to bring to your attention interesting and important information about the safety profile of the medicines you use in practice. You may have even seen the 6-month summary of *Drug Safety Update* advice that was inserted as a leaflet in the March 2008 edition of the BNF: a quick-reference guide for you and your colleagues on our most important advice published August 2007 to March 2008.

We remain committed to helping you stay up to date on the latest safety information for medicines. Preparation for the first issue of volume 2 is under way, and we will continue to listen to your feedback.

This month, we return to the safety of the newest medicine to aid smoking cessation: varenicline (past articles on varenicline were included in the December 2007 and February 2008 issues of *Drug Safety Update*). A wide range of healthcare professionals should find our latest advice on varenicline essential reading. Suicide-related events have been reported in patients using varenicline who are trying to stop smoking. Importantly, cases have been reported for people with no known pre-existing psychiatric conditions, and for people who continued to smoke. Find out more on page 2. Don't forget that we welcome reports on any suspected adverse drug reactions for any medicine—you can complete a Yellow Card online at www.yellowcard.gov.uk.

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: suicidal thoughts and behaviour

Keywords: varenicline, Champix ▼, smoking cessation, suicide-related events

Suicidal thoughts and behaviour have been reported in users of varenicline who have no known pre-existing psychiatric conditions, and while they continue to smoke. Anyone taking varenicline who develops depression or suicidal thoughts should stop their treatment and contact their doctor immediately

Varenicline (Champix ▼) is an 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 March 2008, about 366 000 people had used varenicline in the UK.

Suicidal thoughts and behaviour

Stopping smoking—with or without medication—may be associated with various psychiatric symptoms, such as depressed mood, irritability, anxiety, frustration, or anger. Moreover, stopping smoking may exacerbate an underlying psychiatric condition.

Recently, concerns have arisen about reports of suicidal ideation and suicidal behaviour associated with the use of varenicline. Up to March 18, 2008, we have received 129 reports of suicidal thoughts or behaviour associated with the use of varenicline:

Suicide-related event	Number of events
Completed suicide	2
Suicide attempt	4
Suicidal behaviour	4
Suicidal ideation	118
Suicidal depression	5

Footnote: Note that the sum of the number of suicide-related events exceeds the total number of reports of suicide-related events for varenicline because some reports may contain more than one suicide-related event.

These reports mainly involved people who had pre-existing psychiatric conditions or other psychosocial risk factors. However, a detailed review of UK Yellow Card data found that 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.

Product information for doctors and patients has been updated to reflect these additional findings.

Advice for healthcare professionals:

- Patients should be told to stop treatment and contact their doctor immediately if they develop suicidal thoughts or behaviour
- Varenicline should be stopped immediately if agitation, depressed mood, or changes in behaviour are observed that are of concern to the patient, family, or caregivers
- The safety and efficacy of varenicline in people with serious psychiatric illness have not been established. Patients who have a history of psychiatric illness should be monitored closely while taking varenicline

Complete a Yellow Card online at
www.yellowcard.gov.uk

Please continue to report to us via the Yellow Card scheme all reactions that 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.

To help us with our further evaluation of this issue we ask that when reporting suicide-related events for varenicline, please include the following information where known:

- Smoking status at the time of onset of the event
- Presence or absence of any relevant pre-existing psychiatric illness
- Presence or absence of any significant psychosocial stressors
- Information on previous smoking-cessation attempts: smoking-cessation aids used (if any) and any nicotine-withdrawal symptoms or adverse effects experienced

Bisphosphonates: atrial fibrillation

Keywords: bisphosphonates, zoledronic acid, Aclasta▼, Zometa, alendronic acid, pamidronic acid, osteoporosis, Paget's disease, anticancer, atrial fibrillation

Clinical trial results have suggested an increased risk of atrial fibrillation for zoledronic acid (Aclasta▼), pamidronic acid, and possibly for alendronic acid. The balance of risks and benefits for bisphosphonates remains favourable

Bisphosphonates are used for: prophylaxis and treatment of osteoporosis; treatment of Paget's disease; and as part of some anticancer regimens.

A clinical trial found an increased incidence of atrial fibrillation in women treated with once-yearly zoledronic acid (Aclasta▼).¹ Furthermore, a review of the Fracture Intervention Trial for alendronic acid showed a non-significant trend toward an increased risk of atrial fibrillation in patients treated with alendronic acid.²

These concerns have led to a Europe-wide review of bisphosphonates and atrial fibrillation, including review of clinical-trial data, spontaneous reports of suspected adverse drug reactions, and published literature. This review included two recently published observational studies on alendronic acid and the risk of atrial fibrillation, which had conflicting results.^{3,4} The conclusions of the review are given below.

1 Black DM, et al. *N Engl J Med* 2007; **356**: 1809–22.

2 Cummings SR, et al. *N Engl J Med* 2007; **356**: 1895–96.

3 Sørensen HT, et al. *BMJ* 2008; **336**: 813–16.

4 Heckbert AR, et al. *Arch Intern Med* 2008; **168**: 826–31.

Information for healthcare professionals:

- The risk of atrial fibrillation in association with bisphosphonate treatment seems to be low, and the balance of risks and benefits for bisphosphonates remains favourable
- To date, clinical trial results have suggested an increased risk of atrial fibrillation for zoledronic acid (Aclasta▼), pamidronic acid, and possibly for alendronic acid
- The product information for zoledronic acid has been updated to include atrial fibrillation as a possible side-effect (both for Aclasta▼ and Zometa, a product that contains zoledronic acid that is given every 3–4 weeks as part of cancer treatment). Atrial fibrillation is also being added to the product information for pamidronic acid
- The risk of atrial fibrillation with alendronic acid will be kept under close review. Should further evidence accumulate, the product information for alendronic acid will be updated accordingly

Yellow Card Scheme update

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

Complete a Yellow Card online at www.yellowcard.gov.uk

For information on black triangle drugs see <http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Medicines/Reportingsuspectedadversedrugreactions/Healthcareprofessionalreporting/BlackTriangleScheme/index.htm>

For further information about biosimilar medicines, see *Drug Safety Update* February 2008, p 8. www.mhra.gov.uk/mhra/drugsafetyupdate

For information on guidelines on what to include on a Yellow Card report, see <https://yellowcard.mhra.gov.uk/hcp/hcp-guidelines/> for healthcare professionals, and see <https://yellowcard.mhra.gov.uk/mop/mop-guidelines/> for members of the public

Black triangle: symbol for intensively monitored drugs or vaccines ▼

An important aspect of the reports we receive via the Yellow Card Scheme are suspected adverse reactions associated with drugs that have recently come onto the market. Because relatively limited information about their safety is available new drugs, known as **black triangle drugs** (denoted by an inverted black triangle, ▼), are intensively monitored by the MHRA and the Commission on Human Medicines.

Please help us by reporting any suspected adverse reactions to these new drugs or vaccines. Further information, including a list of drugs that are currently under intensive monitoring, is available on our website.

Black triangle drugs are intensively monitored to ensure that any new safety hazards are identified promptly. A black triangle symbol is assigned to any drug or vaccine that meets any of the following criteria:

- a new active substance or a biosimilar medicine
- a new combination of medicines or active substances
- a new route of administration
- a new drug-delivery system
- an established medicine which is to be used in a new patient population

When a newly licensed medicine is launched onto the market, information about potential adverse effects is limited. Data from clinical trials detect efficacy and the more-common adverse reactions. Effective surveillance after marketing is essential for the identification of rare adverse effects: only when large numbers of patients have taken a medicine can rare or long-term adverse effects be identified.

The black triangle symbol can be found against the relevant drugs that are featured in *Drug Safety Update*. The symbol is also used to identify relevant drugs in the BNF, BNF for children, Nurse Prescribers Formulary, MIMS, ABPI Medicines Compendium, and in advertising material.

Please continue to send us Yellow Cards reports for:

- All adverse reactions associated with black triangle (▼) drugs and vaccines (ie, those new to the market and monitored intensively)
- All adverse reactions in children associated with a drug or vaccine
- All serious adverse reactions associated with established drugs and vaccines
- Suspected delayed drug effects; congenital abnormalities; and adverse drug reactions associated with herbal remedies

Hot topic

This Hot topic article summarises licensed doses, differences in potency between products, and their use with spacer device

Access the Summaries of Product Characteristics at <http://emc.medicines.org.uk/>; access the British Guideline at <http://www.brit-thoracic.org.uk/ClinicalInformation/Asthma/AsthmaGuidelines/tabid/83/Default.aspx>

Access the BNF for Children at <http://bnfc.org/bnfc/>

For further information about asthma management, see our website: <http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Asthma/index.htm>

See <http://emc.medicines.org.uk/>

See <http://www.goldcopd.com/GuidelinesResources.asp?l1=2&l2=0> and <http://www.nice.org.uk/guidance/index.jsp?action=byID&r=true&o=10938>

Recently published evidence on the management of asthma and COPD is summarised by the National Prescribing Centre in its MeReC Stop Press and MeReC Rapid Review blogs. See <http://www.npci.org.uk/blog/>

- 1 *Current Problems in Pharmacovigilance* 2002; **28**: 7. See <http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON007451>
- 2 *Current Problems in Pharmacovigilance* 2006; **31**: 5. See <http://www.mhra.gov.uk/home/groups/pl-p/documents/websitesources/con2023860.pdf>
- 3 *Current Problems in Pharmacovigilance* 2001; **27**: 10. See <http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON007455>
- 4 *Current Problems in Pharmacovigilance* 1998; **24**: 8. See <http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON007473>

Inhaled products that contain corticosteroids

Inhaled corticosteroids are anti-inflammatory medicines that are licensed for the management of asthma and chronic obstructive pulmonary disease. Five corticosteroids are currently available as pressurised metered-dose inhalers: beclometasone; budesonide; ciclesonide; fluticasone; and mometasone; some are available as nebuliser suspensions for inhalation.

Licensed indications

Asthma

All single-constituent inhaled corticosteroids are licensed for the treatment of asthma, and they should be prescribed in accordance with product information (ie, Summary of Product Characteristics) and the British Guideline on the Management of Asthma from the British Thoracic Society and Scottish Intercollegiate Guideline Network.

Not all inhaled corticosteroids are licensed for use in children, particularly high-strength and high-potency formulations;^{1,2} more information is available in the BNF for Children.

The MHRA has previously issued advice about corticosteroid safety.^{3,4} Different inhaled corticosteroids have different potencies. The dose needed for disease control with fluticasone propionate may be lower than that needed with some other inhaled corticosteroids.

Some inhalers contain a corticosteroid and a long-acting beta₂ agonist (LABA) in a fixed-dose combination. All fixed-dose combination inhalers are licensed for the management of asthma.

COPD

Inhaled corticosteroids are not licensed for use alone in the treatment of COPD. However, treatment guidelines suggest that regular use of an inhaled corticosteroid (in addition to bronchodilator therapy) can reduce the frequency of exacerbations for patients with severe COPD (ie, FEV₁ <50% predicted) who have a history of repeated exacerbations.

Please refer to product information for the specific indications and posology of individual products. Seretide 500 Accuhaler and Symbicort 200/6 or 400/12 Turbohaler are licensed for the management of both asthma and COPD.

Different potencies of CFC-free beclometasone inhalers

Qvar and Clenil Modulite▼ are CFC-free pressurised metered-dose inhalers that contain beclometasone dipropionate. They have different potencies because of their different formulations, which may have implications for both safety and efficacy. Qvar has extrafine particles, is more potent than traditional CFC-containing inhalers, and is about twice as potent as Clenil Modulite▼.

Advice for healthcare professionals:

- Prescribe CFC-free beclometasone metered-dose inhalers by brand name to reduce the risk of dosing errors
- Pharmacists are reminded that for any generic prescription for beclometasone, they should establish whether a CFC-free product is required and if so, which brand should be dispensed
- Clenil Modulite▼ may be used in children (with the Volumatic spacer device) and adults; Qvar is not recommended for use in children

Hot topic

CFC-free beclometasone and formoterol

Fostair▼ is a CFC-free, fixed-dose combination of beclometasone and formoterol, which is licensed for the management of asthma in patients aged 18 years or older. Similar to Qvar, Fostair▼ contains an extrafine formulation of beclometasone and is more potent than traditional CFC-containing beclometasone inhalers.

Advice for healthcare professionals:

- The inhaled-corticosteroid component of Fostair▼ is about twice the potency of traditional CFC-containing inhalers, which should be taken into account when switching patients from a non-ultrafine preparation. The dose of beclometasone dipropionate in Fostair▼ should be lower than non-extrafine formulations of beclomethasone dipropionate and will need to be adjusted to the individual needs of the patient

Spacers

Spacers are chambers that can help patients use pressurised metered-dose inhalers more effectively and safely by maximising the amount of medicine that reaches the lung while minimising the amount deposited in the mouth and throat. Spacers are useful for children, patients who need high doses of inhaled corticosteroids, and patients who find it difficult to coordinate actuation of an inhaler with inspiration.

Some of the most commonly used spacers are illustrated below:



Volumatic

For use with Clenil Modulite, Flixotide, and Seretide inhalers



AeroChamber Plus

For use with Alvesco▼ Qvar, and Seretide inhalers



Nebuchamber

For use with Pulmicort inhaler



Able Spacer

See
<http://emc.medicines.org.uk/>

Advice for healthcare professionals:

- Spacers should not be regarded as interchangeable: patients who use a spacer with their inhaler should use the spacer device named in the Summary of Product Characteristics (where specified by name)
- Patients whose asthma is well-controlled and who are using a spacer should always use the same type of spacer and not switch between spacers. Different spacers may deliver different amounts of inhaled corticosteroid, which may have implications for both safety and efficacy

Stop press

Rotigotine patches: new prescribing and storage requirements

For further information, see <http://www.emea.europa.eu/humandocs/PDFs/EPAR/neupro/26875108en.pdf>

Rotigotine (Neupro▼) is a transdermal patch that is indicated for the treatment of the signs and symptoms of early-stage or advanced-stage idiopathic Parkinson's disease. We have recently become aware that the manufacture of rotigotine can result in an alternative crystalline structure of the active ingredient that is visible as a snowflake pattern. Although there is a theoretical possibility that clinical efficacy might be reduced, to date there has been no change in the pattern of suspected adverse reactions reported with this medicine that could be attributed to crystal formation.

Refrigerated storage of the patches seems to reduce crystal development. The Marketing Authorisation Holder will be supplying refrigerated batches to replace products that remain in the distribution chain. Therefore, from the end of July 2008, only 2 mg and 4 mg 24-hour patches will be available for an interim period.

Complete a Yellow Card online at www.yellowcard.gov.uk; contact the Defective Medicines Report Centre at <http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Medicines/Reporting suspected defects in medicines/index.htm>

Advice for healthcare professionals:

- Healthcare professionals should be attentive to any signs that suggest lack of efficacy of rotigotine. Please report any cases of suspected lack of efficacy to us using a Yellow Card. Please report any defects to the Defective Medicines Report Centre
- To prioritise supply for patients who currently take rotigotine, please limit every prescription to 1 month's supply and please do not initiate any new patients on rotigotine
- Inform patients that the patches are currently available and can be used: patients must not stop using their current rotigotine patches, even if they notice snowflake patterns on the patch, without first speaking to a healthcare professional
- Patients must not abruptly stop treatment. Abrupt withdrawal has been associated with a syndrome resembling neuroleptic malignant syndrome or akinetic crisis
- Patients should be advised to store their rotigotine patches in the refrigerator; patches must not be stored in the freezer. Patients should apply and maintain gentle pressure with the palm on the hand for at least 1 min for adhesion; there is no need to bring the patch to room temperature before use



Appearance of an unaffected patch



Appearance of the patch with defect visible as a snowflake pattern

Enoxaparin (Clexane) contamination: latest information

On June 6, 2008, we issued further information about the supply and prescribing of **enoxaparin** (Clexane), see

<http://www.mhra.gov.uk/Publications/Safetywarnings/Drugalerts/CON017989>;
clarification at

<http://www.mhra.gov.uk/Publications/Safetywarnings/Drugalerts/CON018050>.

Ergot-derived dopamine agonists: new warnings and contraindications

The European Medicines Agency has recommended new warnings and contraindications for ergot-derived dopamine agonists as a result of the risk of fibrosis associated with chronic use.

Ergots are mainly used to treat Parkinson's disease. Although fibrosis is a known side-effect of ergots, the Agency's Committee for Medicinal Products for Human Use reviewed new data for an increased risk of fibrosis, particularly cardiac fibrosis, in patients who received ergots as chronic treatment, suggesting that fibrosis can develop before occurrence of symptoms.

The risk of fibrosis is not equally established for all ergots. **Pergolide**, **cabergoline**, and **bromocriptine** are ergots licensed for treatment of Parkinson's disease in the UK. Their product information will be updated as follows:

- **Cabergoline and pergolide:** prescribing information currently has a contraindication for patients with evidence of valve problems and a restriction to second-line use Parkinson's disease.
 - a warning that patients must be monitored for signs of fibrosis on echocardiography before treatment is started and regularly during treatment
 - a reduction of maximum recommended dose to 3 mg a day
 - inclusion of cardiac fibrosis as a very common side-effect
- **Bromocriptine**
 - a contraindication for patients with pre-existing valve problems
 - restriction of maximum dose to 30 mg a day

Advice for healthcare professionals:

- Prescribe ergots according to the updated prescribing information (above)
- Ergots should not be given to patients who have had fibrosis in the heart, lungs, or abdomen. Absence of cardiac fibrosis should be verified before treatment is started
- Monitor patients for signs of fibrosis during treatment by use of blood tests, echocardiography, or chest radiography as appropriate

Etoricoxib: new prescribing guidelines

For further information see
www.emea.europa.eu

The European Medicines Agency has completed a review of the benefits and risks of 90 mg etoricoxib (Arcoxia▼) in the treatment of rheumatoid arthritis and ankylosing spondylitis. The Agency's Committee for Medicinal Products for Human Use has concluded that etoricoxib's benefits outweigh the risks in the treatment of rheumatoid arthritis. Furthermore, the Committee recommended extension of the indication to include ankylosing spondylitis at a dose of 90 mg once a day.

However, the Committee recommended an update to the existing contraindication in patients with inadequately controlled hypertension to state that patients whose blood pressure is persistently above 140/90 mmHg and inadequately controlled must not receive etoricoxib. Furthermore, high blood pressure should be controlled before starting treatment, and should be monitored for 2 weeks after the start of treatment and regularly thereafter.

Advice for healthcare professionals:

- Prescribe etoricoxib in accordance with the above updated product information
- Monitor patients closely for any signs and symptoms of cardiovascular side-effects (eg, fluid retention, high blood pressure, shortness of breath, or chest pain)

Recombinant human erythropoietins: new warning for use in patients with cancer

For further information see:
www.emea.europa.eu

The European Medicines Agency has recommended a new warning for the recombinant human erythropoietins that are authorised for the treatment of patients with anaemia associated with cancer chemotherapy: blood transfusion should be the preferred method for correction of anaemia in these patients, particularly in those whose cancer prognosis is good.

Recombinant human erythropoietins are authorised for the treatment of anaemia in symptomatic patients who have non-myeloid tumours who are receiving chemotherapy. The Agency's Committee for Medicinal Products for Human Use reviewed new published^{1,2} and unpublished data that suggested increased risk of tumour progression, venous thromboembolism, and decreased overall survival in patients with cancer who received recombinant human erythropoietins compared with patients who did not.

The Committee concluded that the benefits of recombinant human erythropoietins continue to outweigh the risks in their approved indications. However, in patients with cancer who have a reasonably long life-expectancy, their benefits may not outweigh the risks of tumour progression and decreased overall survival.

Advice for healthcare professionals:

- The decision to use recombinant human erythropoietins in patients with cancer should be based on an informed assessment of the benefits and risks for a patient, taking into account tumour type and stage, degree of anaemia, life-expectancy, the environment in which the patient is being treated, and patient preference

1 Bennett CL, et al. *JAMA* 2008; **299**: 914–24.

2 Thomas G, et al. *Gynecol Oncol* 2008; **108**: 317–25.

Other information from the MHRA

Patient Information Leaflet of the month: Aldactone

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)

Patient information leaflets (PILs) are improving in quality as a result of new legal obligations on manufacturers to test the documents on potential patients. Testing makes sure that the presentation of the information enables patients to find and understand key messages for safe use about the medicine within the PIL and thereby 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 the PIL for **Aldactone** (spironolactone), a diuretic for treatment of congestive heart failure and for oedema and ascites caused by cirrhosis of the liver.

Access the webpages at
<http://www.mhra.gov.uk/Safetyinformation/Healthcareproviders/Ophthalmologists/C/ON013985>
and
<http://www.mhra.gov.uk/Safetyinformation/Healthcareproviders/Cardiologistssection/index.htm>

New sections on MHRA website for ophthalmologists and cardiologists

We have launched a new series of webpages for targeted groups of healthcare professionals. The first webpage collections in the series are dedicated sections for ophthalmologists and cardiologists. The sections contain recent safety alerts relevant to each professional area, education modules, and details of how to report suspected adverse drug reactions or adverse incidents with medical devices. On developing these webpages, we consulted with some members of relevant professional bodies. Let us know your thoughts on these sections by visiting the feedback section of our website.

Give your feedback at
<http://www.mhra.gov.uk/Yourviews/index.htm>

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

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