

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**

Volume 3, Issue 5 **December 2009**

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As another year draws to a close, we are reflecting on some of the most important drug-safety advice from the bulletin this year. Why not test your drug-safety knowledge in our quiz by turning to p 6, or use the questions as a way to reflect on current areas where your vigilance is important?

This month, we bring you important information in light of the recent licensing of new ciclosporin products in the UK. This narrow therapeutic drug should be prescribed and dispensed by brand: small differences in bioavailability between different formulations could affect ciclosporin blood levels in patients stabilised on a specific brand. For this reason, brands of ciclosporin are not considered interchangeable without careful therapeutic monitoring (p 2).

We have also completed a review of the safety information for all warfarin products. This review has led to the creation of a consistent, core Summary of Product Characteristics for all products to help ensure safer use of this widely used and important medicine. Further details, and a link to the updated information, is given on p 7.

Don't forget that you can tell us about any suspected adverse drug reactions on a Yellow Card. This month, we summarise how to complete a Yellow Card (p 4).

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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 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.

Drug safety advice

Ciclosporin: must be prescribed and dispensed by brand name

Keywords: Ciclosporin, Sandimmun, Neoral, interchangeability, bioequivalence, bioavailability, transplantation, transplant rejection, graft rejection

Patients should be stabilised on a single brand of ciclosporin because switching between formulations without close monitoring may lead to clinically important changes in bioavailability. All products that contain ciclosporin are interchangeable **only if careful therapeutic monitoring takes place. Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent switching**

Ciclosporin: narrow therapeutic index

Ciclosporin is a critical-dose drug with a narrow therapeutic index. It is indicated for the prevention and treatment of transplant rejection, psoriasis, atopic dermatitis, rheumatoid arthritis, and nephrotic syndrome. The established brands are Neoral (available as an oral solution or as soft gelatin capsules) and Sandimmun (available as an oral solution, concentrate for infusion, or as soft gelatin capsules). In line with advice from the British National Formulary, oral versions of Sandimmun are only administered on a named-patient basis for those who cannot be transferred to another brand of oral ciclosporin. The capsules and oral solution should be given twice a day; all doses are based on patient weight.

See www.bnf.org

Availability of new ciclosporin products

A number of new versions of ciclosporin-containing products have been granted marketing authorisations (licences) in the UK. As at October 2009, one new product range (25 mg, 50 mg, and 100 mg capsules) has been launched. The bioequivalence of these new products has been shown with the reference product, Neoral, in studies using healthy volunteers.

However, because of the critical-dose nature of the drug, even minor differences in bioavailability could affect ciclosporin blood levels in patients stabilised on a specific brand or formulation. This difference could potentially lead to organ rejection. Therefore, the new ciclosporin products that have been granted marketing authorisations in the UK have been approved with a specific brand name.

All products that contain ciclosporin should be prescribed by brand name to minimise the risk of inadvertent switching between brands, and to reflect advice in the British National Formulary.

Important safety information for safe use of ciclosporin products

Prescribers, pharmacists, and patients should be aware that substitution with any other oral brand or formulation of ciclosporin is not recommended without careful therapeutic monitoring because this may alter ciclosporin blood levels. Particular care should be taken to prescribe and dispense the same brand of ciclosporin. Prescribers, pharmacists, and patients should be fully aware of the brand prescribed.

Brands of ciclosporin are not considered interchangeable without careful therapeutic monitoring. If switching of a patient stabilised to one brand of ciclosporin is unavoidable, the patient should be closely monitored for side effects, ciclosporin drug blood concentrations, serum creatinine levels, blood pressure, and transplant function.

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Advice for healthcare professionals:

- Ciclosporin is a critical-dose drug with a narrow therapeutic index
- Care should be taken to stabilise the patient on a single brand of ciclosporin, and to ensure that the same brand of ciclosporin is always prescribed and dispensed to the patient
- When switching of a patient stabilised to one brand of ciclosporin is unavoidable, the patient should be closely monitored for side effects, drug blood concentrations, and transplant function

Finasteride: potential risk of male breast cancer

Keywords: finasteride, Proscar, Propecia, benign prostatic hyperplasia, BPH, male breast cancer, alopecia, hair loss

Cases of male breast cancer have been reported for finasteride. Patients should be advised to promptly report to their doctor any changes in their breast tissue such as lumps, pain, or nipple discharge

Finasteride is an inhibitor of type II 5 α -reductase, an enzyme that metabolises testosterone into the more potent androgen, dihydrotestosterone (DHT), resulting in a reduction in DHT concentrations in serum and target tissues. 5 mg finasteride (Proscar) is used for the treatment and control of benign prostatic hyperplasia because enlargement of the prostate gland is dependent on conversion of testosterone to DHT. Finasteride can also reduce scalp and serum DHT concentrations, and the 1 mg dose (Propecia) is indicated for the treatment of men with androgenetic alopecia to increase hair growth and prevent further hair loss.

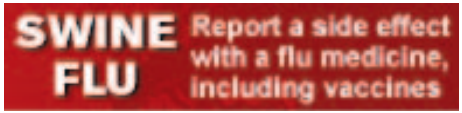
Up to November 2009, 50 cases of male breast cancer have been reported worldwide with 5 mg finasteride and three cases with the 1 mg dose. Overall, the incidence of male breast cancer in clinical trials for 5 mg finasteride was not significantly increased: 7.8 per 100 000 patient-years (95% CI 3.7–16.4) for patients exposed to finasteride for more than 1 year compared with 3.8 per 100 000 patient-years (1.2–11.9) for those not exposed to finasteride.

The mechanism of action of finasteride (inhibition of type II 5 α -reductase) leads to decreases in DHT levels that are accompanied by increases in testosterone and oestradiol levels. Although no change in the testosterone to oestradiol ratio is observed, this could have implications for a potentially increased risk of breast cancer. A review of available data suggests that an increased risk of breast cancer with finasteride cannot be excluded.

Further information is available in an MHRA assessment report available at <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/index.htm>

Advice for healthcare professionals:

- Cases of male breast cancer have been reported in clinical trials (Proscar) and during post-marketing use (Proscar and Propecia) with finasteride treatment
- Patients should be advised to promptly report to their doctor any changes in their breast tissue such as lumps, pain, or nipple discharge



Reporting suspected adverse reactions to flu antivirals and flu vaccines

Please remember that you can report suspected adverse reactions to **flu antivirals** (oseltamivir [Tamiflu] and zanamivir [Relenza]), and to **flu vaccines** (the new H1N1 vaccines Pandemrix and Celvapan, and the seasonal vaccines) online at www.mhra.gov.uk/swineflu

Every report of a suspected side effect remains vital for the real-time safety monitoring of these products. If in doubt, please report anyway.

Further information, including weekly summaries of the latest adverse-reaction data for these products, is available at www.mhra.gov.uk/swineflu

Yellow Card Scheme update

How to complete a Yellow Card

You can complete a Yellow Card to tell us about a suspected adverse drug reaction to any medicine. Yellow Cards can be found in the back of the British National Formulary. Alternatively it is easier to report online at www.yellowcard.gov.uk.

This is an example of a Yellow Card showing the minimum information which must be completed. This is all the information you need to make a report, although additional detail helps us assess the case.

Yellowcard [®]		In Confidence		MHRA																			
COMMISSION ON HUMAN MEDICINES		SUSPECTED ADVERSE DRUG REACTIONS																					
If you suspect that an adverse reaction may be related to a drug, or a combination of drugs, you should complete this Yellow Card or complete a report on the website at www.yellowcard.gov.uk . For <i>intensively monitored medicines</i> (identified by ▼) report all suspected reactions (including any considered not to be serious). For <i>established drugs</i> and <i>herbal remedies</i> report all serious adverse reactions in adults; report all serious and minor adverse reactions in children (under 18 years). You do not have to be certain about causality: if in doubt, please report. Do not be put off reporting just because some details are not known. See BNFC (page 21) or the MHRA website (www.yellowcard.gov.uk) for additional advice.																							
PATIENT DETAILS Patient Initials: <u>N B</u> Sex: <u>M</u> <u>F</u> Weight if known (kg): _____ Age (at time of reaction): _____ Identification (Your Practice / Hospital Ref.): _____																							
SUSPECTED DRUG(S) Give brand name of drug and batch number if known <table border="1"> <thead> <tr> <th>Brand name</th> <th>Route</th> <th>Dosage</th> <th>Date started</th> <th>Date stopped</th> <th>Prescribed for</th> </tr> </thead> <tbody> <tr> <td><u>COMBIVIR</u></td> <td><u>PO</u></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td><u>SIMVASTATIN</u></td> <td><u>PO</u></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>						Brand name	Route	Dosage	Date started	Date stopped	Prescribed for	<u>COMBIVIR</u>	<u>PO</u>					<u>SIMVASTATIN</u>	<u>PO</u>				
Brand name	Route	Dosage	Date started	Date stopped	Prescribed for																		
<u>COMBIVIR</u>	<u>PO</u>																						
<u>SIMVASTATIN</u>	<u>PO</u>																						
SUSPECTED REACTION(S) Please describe the reaction(s) and any treatment given: <u>Blistering of lips and mouth</u>																							
Date reaction(s) started: _____ Date reaction(s) stopped: _____ Do you consider the reaction to be serious? Yes / No _____ If yes, please indicate why the reaction is considered to be serious (please tick all that apply): Patient died due to reaction <input type="checkbox"/> Involved or prolonged inpatient hospitalisation <input type="checkbox"/> Life threatening <input type="checkbox"/> Involved persistent or significant disability or incapacity <input type="checkbox"/> Congenital abnormality <input type="checkbox"/> Medically significant, please give details: _____																							
* This is to enable you to identify the patient in any future correspondence concerning this report																							

1. At least one piece of patient information is required, and can be any of: **age; sex; weight; initials; height; or a local identification number**

2. The name of one or more suspect drug(s) thought to have caused the adverse drug reaction is required

3. Describe the suspected adverse drug reaction

Please attach additional pages if necessary

Please list other drugs taken in the last 3 months prior to the reaction (including self-medication & herbal remedies) Was the patient on any other medication? Yes / No If yes, please give the following information if known: <table border="1"> <thead> <tr> <th>Drug (Brand, if known)</th> <th>Route</th> <th>Dosage</th> <th>Date started</th> <th>Date stopped</th> <th>Prescribed for</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>						Drug (Brand, if known)	Route	Dosage	Date started	Date stopped	Prescribed for						
Drug (Brand, if known)	Route	Dosage	Date started	Date stopped	Prescribed for												
Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed), suspected drug interactions. For congenital abnormalities please state all other drugs taken during pregnancy and the date of the last menstrual period.																	
REPORTER DETAILS Name and Professional Address: <u>A. N. Other</u> <u>Wharfedale HIV Clinic</u> <u>Sf Martins Hospital</u> Post code: <u>S12 0DB</u> Tel No: <u>0207 12345678</u> Speciality: <u>GUM/HIV nurse</u> Signature: _____ Date: _____			CLINICIAN (if not the reporter) Name and Professional Address: _____ _____ _____ Tel No: _____ Post code: _____ Speciality: _____ If you would like information about other adverse reactions associated with the suspected drug, please tick this box <input type="checkbox"/>														
If you report from an area served by a Yellow Card Centre (YCC), MHRA may ask the Centre to communicate with you, on its behalf, about your report. See BNFC (page 21) for further details on YCCs. If you want only MHRA to contact you, please tick this box. <input type="checkbox"/>																	

Send to Medicines and Healthcare products Regulatory Agency, CHM FREEPOST, LONDON SW8 5BR

4. The contact details of the reporter must be provided. These are held in strict confidence, and are only used to contact the reporter when additional information is required. Reporter details are not provided to any third party

...continued

Below is a more-complete version of the same Yellow Card. The additional information provided by the reporter helps with the assessment of the case, and allows correlation with the details of other cases.

Yellowcard
COMMISSION ON HUMAN MEDICINES

In Confidence

MHRA

SUSPECTED ADVERSE DRUG REACTIONS

If you suspect that an adverse reaction may be related to a drug, or a combination of drugs, you should complete this Yellow Card or complete a report on the website at www.yellowcard.gov.uk. For *intensively monitored medicines* (identified by ▼) report **all** suspected reactions (including any considered not to be serious). For *established drugs and herbal remedies* report **all serious** adverse reactions in adults; report **all serious and minor** adverse reactions in **children** (under 18 years). You do not have to be certain about causality; if in doubt, please report. Do not be put off reporting just because some details are not known. See BNFC (page 21) or the MHRA website (www.yellowcard.gov.uk) for additional advice.

PATIENT DETAILS		Patient Initials: <u>N B</u>	Sex: M <input type="radio"/> F <input checked="" type="radio"/>	Weight if known (kg): _____
Age (at time of reaction): _____		Identification (Your Practice / Hospital Ref)*: _____		
SUSPECTED DRUG(S)				
Give brand name of drug and batch number if known				
<u>COMBIVIR</u>	Route <u>PO</u>	Dosage <u>1 tab OD</u>	Date started <u>12/6/08</u>	Date stopped <u>14/7/08</u>
<u>ZOCOR</u>	<u>PO</u>	<u>10mg OD</u>	<u>12/6/08</u>	<u>14/7/08</u>
Prescribed for <u>HIV prophylaxis</u> <u>High cholesterol</u>				
SUSPECTED REACTION(S)				
Please describe the reaction(s) and any treatment given: <u>Blistering of lips and mouth</u>				
<u>Tingling of face. Possible Stevens Johnson Syndrome?</u>				
Date reaction(s) started: <u>14/7/08</u> Date reaction(s) stopped: _____				
Do you consider the reaction to be serious? Yes <input checked="" type="checkbox"/> / No <input type="checkbox"/>				
If yes, please indicate why the reaction is considered to be serious (please tick all that apply):				
Patient died due to reaction <input type="checkbox"/>	Involved or prolonged inpatient hospitalisation <input type="checkbox"/>			Recovered <input type="checkbox"/>
Life threatening <input type="checkbox"/>	Involved persistent or significant disability or incapacity <input type="checkbox"/>			Recovering <input type="checkbox"/>
Congenital abnormality <input type="checkbox"/>	Medically significant; please give details: <u>? SJS</u>			Continuing <input checked="" type="checkbox"/>
Other <input type="checkbox"/>				

* This is to enable you to identify the patient in any future correspondence concerning this report

1. Full details of the suspect drugs have been provided. The dates allow us to calculate duration of treatment and time to onset of the reaction

2. Brand names of drug should be provided if known

3. Further details of the adverse drug reaction have been provided, including the outcome

4. The reporter has provided their assessment of the seriousness of the reactions—here considered to have caused the patient to be hospitalised, and also to be medically significant

Please attach additional pages if necessary

Please list other drugs taken in the last 3 months prior to the reaction (including self-medication & herbal remedies)				
Was the patient on any other medication? Yes / No If yes, please give the following information if known:				
Drug (Brand, if known)	Route	Dosage	Date started	Date stopped
<u>KALETRA</u>	<u>PO</u>	<u>3 tabs BD</u>	<u>12/6/08</u>	<u>---</u>
<u>FOSAMPRENAVIR</u>	<u>PO</u>	<u>1200 mg BD</u>	<u>12/6/08</u>	<u>---</u>
Prescribed for <u>HIV prophylaxis</u>				
Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed), suspected drug interactions. For congenital abnormalities please state all other drugs taken during pregnancy and the date of the last menstrual period.				
<u>Anaphylactic shock in 2006. Allergy to penicillin.</u>				
<u>No other relevant history</u>				
<u>3/6/08 CD4 cell count 1240 per mL³</u> <u>3/6/08 HIV viral load 550 copies/mL</u>				
REPORTER DETAILS			CLINICIAN (if not the reporter)	
Name and Professional Address: <u>A. N. Other</u>			Name and Professional Address: _____	
<u>Wharfedale HIV Clinic</u>			Post code: _____	
<u>St Martins Hospital</u>			Speciality: _____	
Post code: <u>S12 0DB</u>	Tel No: <u>0207 12345678</u>		Tel No: _____	
Speciality: <u>GUM/HIV nurse</u>	Date: _____		If you would like information about other adverse reactions associated with the suspected drug, please tick this box <input type="checkbox"/>	
Signature: <u>[Signature]</u>			If you report from an area served by a Yellow Card Centre (YCC), MHRA may ask the Centre to communicate with you, on its behalf, about your report. See BNFC (page 21) for further details on YCCs. If you want only MHRA to contact you, please tick this box. <input type="checkbox"/>	

Send to Medicines and Healthcare products Regulatory Agency, CHM FREEPOST, LONDON SW8 5BR

5. Concomitant medicines taken in the past 3 months have been included

6. The reporter has also included some additional information on the indication, and has also reported that there is no other relevant history. This information helps prevent unnecessary follow-up with the reporter for patient history when it is unavailable

7. For reports of patients with HIV, the HIV viral load and CD4 T-cell count are useful for assessment of the patient's disease status

Quiz

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

Do you read Drug Safety Update every month? Then test your knowledge of drug safety in our annual quiz.

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

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

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

- Q1:** The immunosuppressant **tacrolimus** is available as an immediate-release formulation (brand name Prograf, given twice daily) and as a prolonged-release formulation (brand name Advagraf, given once daily). Why is it important not to switch between formulations without specialist supervision and monitoring?
- Q2:** Which types of cancer would contraindicate use of the synthetic hormone therapy **tibolone**? List the approved indications for this drug.
- Q3:** What is the minimum age for which **methylphenidate** is licensed for ADHD? How often should treatment be interrupted to determine whether continuation is needed?
- Q4:** What are the key risks of **antipsychotic** use in elderly people with dementia?
- Q5:** Case reports of pancreatitis have been reported for the type 2 diabetes treatment **exenatide**. What action should you take if pancreatitis is suspected? Diabetes is often complicated by renal dysfunction; for which patients is exenatide **not** recommended?
- Q6:** Atypical stress fractures of the proximal femoral shaft have been reported in patients treated long-term with the **bisphosphonate alendronic acid**. Name one characteristic of these fractures, and what action should you take in patients who develop these fractures during treatment?
- Q7: Topical oral salicylate pain-relief gels** are contraindicated in those younger than age...
- a) 2 years b) 5 years c) 16 years?
- What is the reason for this contraindication?
- Q8:** Over-the-counter medicines that contain **codeine** or **dihydrocodeine** are indicated for the short-term treatment of acute, moderate pain which is not relieved by paracetamol, ibuprofen, or aspirin alone. What is the maximum recommended duration of treatment without healthcare-professional advice?
- a) 3 days b) 5 days c) 7 days
- Q9:** In the UK, is **aspirin** licensed for primary prevention of thrombotic vascular disease (ie, in people without a history of vascular disease such as ischaemic heart disease or cerebrovascular disease)?
- Q10:** If a drug or vaccine has a black triangle symbol (▼), what implications does this have in relation to the reporting of suspected adverse reactions via the Yellow Card Scheme? How does this differ from drugs and vaccines that do not have a black triangle?

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

Stop press

Etravirine: reports of severe hypersensitivity reactions

Etravirine (Intelence ▼), in combination with a boosted protease inhibitor and other antiretrovirals, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults.

Cases of severe hypersensitivity syndromes, including drug rash with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN), sometimes fatal, have been reported with etravirine.

Etravirine must be immediately discontinued if severe rash or hypersensitivity reaction is suspected. Delay in stopping treatment after the onset of severe rash may result in a life-threatening reaction. Patients who have stopped treatment because of hypersensitivity reactions should not restart etravirine.

Please report all suspected adverse reactions to etravirine on a Yellow Card at www.yellowcard.gov.uk

Further information is provided in a letter to healthcare professionals sent in October 2009 available at <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON062566>

Rituximab: progressive multifocal leukoencephalopathy in a patient without prior treatment for rheumatoid arthritis

Rituximab (MabThera) in combination with methotrexate is indicated for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying antirheumatic drugs including one or more tumour necrosis factor (TNF) inhibitor therapies. Rituximab is also indicated for treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia in combination with chemotherapy.

In September 2009, a case of progressive multifocal leukoencephalopathy (PML) with a fatal outcome was reported in a patient with rheumatoid arthritis who had not previously received treatment with methotrexate or a TNF antagonist. This case is the third case of PML reported in a patient with rheumatoid arthritis who was receiving rituximab. Cases of PML have also been reported in patients with other autoimmune diseases treated with rituximab.

A letter has been sent to relevant healthcare professionals to inform of this case and to remind that rituximab is not indicated for first-line treatment of rheumatoid arthritis.

Access the letter sent in November 2009 at <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm>

Warfarin: product information to be amended to give clearer, up-to-date advice

We continue to receive a substantial number of serious and fatal adverse event reports for **warfarin** through our Yellow Card Scheme.

We have recently reviewed the safety information for warfarin products to assess whether it is in line with information from Yellow Card reports, the current medical literature, and with current practice guidance. No new safety issues were identified during this review; however, the Summaries of Product Characteristics (SPCs) for all warfarin products are to be amended to give clearer and up-to-date advice to healthcare professionals. This update will also result in improved patient leaflets to ensure patients have consistent and appropriate information on this important medicine.

In particular, the core SPC provides advice on:

- Timing of warfarin treatment after ischaemic stroke
- Management of the patient before surgical or dental procedures
- Patients at particular risk of haemorrhage
- Interactions with herbal products, foods, and food supplements
- Management of patients with significantly raised INR and/or haemorrhage

Continues...

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Access the public assessment report at <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/index.htm>

Further information on the safer use of anticoagulant therapy is available from the National Patient Safety Agency at <http://www.nrls.npsa.nhs.uk/resources/?entryid45=59814>

The updated warfarin core safety information, along with further information on the review, is available in a public assessment report on our website. In particular, healthcare professionals should ensure that they understand the contraindications to warfarin therapy, the relevant warnings, and the clinically significant drug interactions. Serious and unexpected adverse effects relating to warfarin should continue to be reported via the Yellow Card Scheme (www.yellowcard.gov.uk).

Drug alert: recall of Gaviscon Advance Peppermint Flavour, Boots Heartburn Relief Peppermint Flavour, Peptac Peppermint Liquid, and Peptac Liquid Aniseed Flavour

The following batches of medicine are being recalled from the market because of low levels of microbial contamination:

	Batch number(s)*
Gaviscon Advance Peppermint Flavour†	924471 and 925071
Boots Heartburn Relief Peppermint Flavour‡	41808
Peptac Peppermint Liquid‡	41808 and 41957
Peptac Liquid Aniseed Flavour‡	41757

*All are 500 mL bottles. †A low proportion of bottles in batch 924471 are known to be affected and batch 925071 is being recalled as a precautionary measure (although no bottles in this batch are reported defective). ‡Precautionary recall due to low-level microbial contamination detected in a small number of samples from these batches.

The causes of the contaminations are under investigation and are unlikely to be harmful to normally healthy consumers. However, if these products are being used by patients with suppressed immune systems (eg, those receiving chemotherapy), the risk of infection and other adverse reactions cannot be ruled out. GPs or pharmacists receiving enquiries from such patients are requested to give professional advice and refer to the responsible treatment centre where necessary.

Further information is available at <http://www.mhra.gov.uk/Publications/Safetywarnings/DrugAlerts/CON062825> and <http://www.mhra.gov.uk/Publications/Safetywarnings/DrugAlerts/CON062892>

Other information from the MHRA

Patient Information Leaflet of the month: Arthrotec

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 enables 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 **Arthrotec**, which contains **diclofenac and misoprostol** and is used in the treatment of rheumatoid arthritis and osteoarthritis. These leaflets demonstrate how the serious side effects associated with this medicine can be displayed prominently for easy access by patients.

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)

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

Sign up to receive an email alert when a new issue is published: email registration@mhradrugsafety.org.uk

Report a suspected adverse drug reaction at www.yellowcard.gov.uk

Quiz answers

- Q1A:** **Tacrolimus** has a narrow therapeutic index. Medication errors have been reported, which in some cases resulted in patients being dosed incorrectly, leading to serious adverse reactions and in some cases graft rejection (January issue, p 4).
- Q2A:** **Tibolone** is contraindicated in women with known or suspected breast cancer, and in those with a history of breast cancer. Tibolone is also contraindicated in women with oestrogen-dependent cancers, such as endometrial cancer. Tibolone is indicated as first-line treatment for menopausal symptoms, and as second-line for prevention of osteoporosis in postmenopausal women at high fracture risk. Although anecdotal evidence suggests tibolone is sometimes used for treatment of vasomotor symptoms in women with a history of breast cancer, such use is off-label: in a randomised placebo-controlled trial in women with breast cancer, tibolone increased the risk of breast cancer recurrence (February issue, p 2).
- Q3A:** **Methylphenidate** is licensed for treatment of ADHD in children age 6 years or older and adolescents. Treatment should be interrupted at least once a year to determine whether continuation is needed (March issue, p 2).
- Q4A:** In elderly people with dementia, **antipsychotic** use is associated with a clear increased risk of stroke and a small increased risk of death. Only one antipsychotic, risperidone (Risperdal ▼), is licensed for treatment of dementia-related behavioural disturbances: and then only for short-term (up to 6 weeks') treatment of persistent aggression in Alzheimer's dementia unresponsive to non-pharmacological approaches and where there is a risk of harm to the patient or others (March issue, p 5).
- Q5A:** If pancreatitis is suspected, **exenatide** should be suspended immediately; if pancreatitis is confirmed, it should be permanently discontinued. Exenatide is not recommended for patients with end-stage renal disease or with severe renal impairment (creatinine clearance <30 mL/min; case reports of renal impairment have been received, March issue p 6).
- Q6A:** Characteristics of atypical stress fractures: occur after minimal or no trauma; patients may experience thigh pain weeks to months before presenting with a completed femoral fracture; frequently bilateral; poor healing. In patients who develop these fractures during treatment, discontinue **alendronic acid** and give no further **bisphosphonate** treatment unless benefits of continued treatment clearly outweigh the risks. An increased risk of atypical stress fractures with other bisphosphonates cannot be ruled out (March issue, p 8).
- Q7A:** Age 16 years, because of a theoretical risk of Reye's syndrome. The contraindication is consistent with current advice on aspirin (June issue, p 4).
- Q8A:** 3 days. OTC medicines containing **codeine** or **dihydrocodeine** can cause addiction or overuse headache if used continuously for more than 3 days (September issue, p 6).
- Q9A:** No. In the UK, low-dose **aspirin** is licensed for prevention of thrombotic cerebrovascular or cardiovascular disease only in those who already have vascular disease (ie, secondary prevention). In primary prevention the absolute risk of a serious vascular event is far lower than in secondary prevention and any vascular event benefit of aspirin is likely to be at least partly offset by the small increase in serious bleeding events (October issue, p 10).
- Q10A:** All suspected adverse reactions should be reported for black triangle drugs and vaccines. Only serious adverse reactions need be reported for established drugs and vaccines that do not have a black triangle. If you are unsure whether to report, you should do so (see www.yellowcard.gov.uk).

How did you score?

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