

# 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.

Welcome to the first issue of volume 2 of Drug Safety Update. As Drug Safety Update enters its second year, we continue with: important updates and reminders about drug-safety advice (p 2–3); information about the Yellow Card Scheme for reporting of suspected adverse drug reactions (p 4; [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)); monthly hot topics of interest (p 5); a brief round-up of emerging safety information (p 7); and other information about our work here at the MHRA (p 8).

This month, we focus on new information for antiepileptic medicines. Evidence from a Europe-wide review and from a published meta-analysis of clinical trials suggests that antiepileptic treatment is associated with a small increased risk of suicidal thoughts and behaviour. We advise that patients and caregivers should be alert to signs of these adverse effects throughout treatment, and that patients should be referred for appropriate treatment if necessary (p 2).

Also this month we highlight the safeguards in place for two new medicines for the treatment of multiple myeloma—thalidomide and lenalidomide. Read more on p 5.

Don't forget that you can register to receive a monthly email reminder when a new issue of Drug Safety Update is published. Simply send an email to [registration@mhradrugsafety.org.uk](mailto:registration@mhradrugsafety.org.uk)

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# Drug safety advice

## Antiepileptics: risk of suicidal thoughts and behaviour

**Keywords:** antiepileptics, epilepsy, psychiatric disorders, suicidal thoughts, suicidal behaviour

Antiepileptic treatment is associated with a small increased risk of suicidal thoughts and behaviour. Patients and caregivers should be alert to signs of suicidal thoughts or behaviour throughout treatment

For further information, including a question and answer sheet for patients, see <http://www.mhra.gov.uk/Safetyinformation/index.htm>

### Antiepileptic medicines:

- carbamazepine
- divalproex sodium
- felbamate
- gabapentin
- lamotrigine
- levetiracetam\*
- oxcarbazepine
- pregabalin
- tiagabine
- topiramate\*
- vigabatrin\*
- zonisamide\*

\* These medicines already have advice and warnings about suicidal thoughts and behaviour

See FDA Public Health Advisory, January 2008  
<http://www.fda.gov/cder/drug/InfoSheets/HCP/antiepilepticsHCP.htm>

For further information about the FDA analyses see  
<http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf>

Concern about a possible risk of suicidal thoughts and behaviour associated with antiepileptics led to a Europe-wide review of data from clinical trials, published literature, and postmarketing spontaneous reports of adverse drug reactions. This review has concluded that any antiepileptic drug may rarely be associated with a small increased risk of suicidal thoughts and behaviour.

Some product information already has advice and warnings; product information for all antiepileptics is being updated to reflect the most recent data, and to highlight the need for monitoring of patients for development of suicidal thoughts or behaviour.

The findings of the Europe-wide review took into account a published meta-analysis from the US Food and Drug Administration. This included placebo-controlled trials for 11 antiepileptic drugs (a total of 199 trials involving 43 800 patients) indicated for epilepsy; psychiatric disorders (including bipolar disorder, schizophrenia, and anxiety); or other disorders (including neuropathic pain). The findings show an increased risk of suicidal thoughts and behaviour in those who received antiepileptics compared with those who received placebo. The increased risk was generally recorded for all drugs studied and was evident as early as 1 week after starting treatment. 0.43% of patients who received antiepileptics had suicidal thoughts and behaviour compared with 0.22% of patients who received placebo. Approximately two additional patients per 1000 in the antiepileptic group had such an event compared with the placebo group. Increased risk could not be attributed to particular patients. In particular, there was no clear pattern of risk across age-groups.

### Advice for healthcare professionals:

- Antiepileptic treatment is associated with a small risk of suicidal thoughts and behaviour; available data suggest that the increased risk applies to all antiepileptics and is seen as early as 1 week after starting treatment
- Patients should be alert to any mood changes, distressing thoughts, or feelings about suicide or harming themselves at any point during treatment. They should be advised to seek medical advice if they develop such thoughts or behaviour, and should be referred for appropriate treatment if necessary
- The available evidence does not define whether the risk of suicidal thoughts and behaviour differs between antiepileptics. Patients should not stop or switch treatment on the basis of this information and without speaking to a healthcare professional

## Recombinant human erythropoietins: new recommendations for treatment of anaemia in cancer

**Keywords:** Recombinant human erythropoietins, epoetin, erythropoiesis, cancer, anaemia, haemoglobin, tumour progression, survival

Available evidence suggests that patients with cancer who receive recombinant human erythropoietins have an increased risk of tumour progression and reduced overall survival. The decision to administer recombinant erythropoietins should be based on an informed benefit-risk assessment with the participation of the patient. Factors to consider should include tumour type and stage; degree of anaemia; life-expectancy; the environment in which the patient is being treated; and the patient's preference

Five r-HuEPOs are authorised in the UK:

- epoetin alfa (Eprex)
- darbepoetin alfa (Aranesp)
- epoetin beta (NeoRecormon)
- epoetin delta (Dynepo ▼)
- methoxy polyethylene glycol-epoetin beta (Mircera ▼)

Biosimilar analogues of epoetin alfa have also been licensed in the EU and may be marketed in the UK (Abseamed ▼, Binocrit ▼, Epoetin alfa Hexal ▼)

Access information on r-HuEPOs in European Public Assessment Reports available at <http://www.emea.europa.eu/htms/human/epar/a.htm>;  
Summaries of Product Characteristics are available at <http://emc.medicines.org.uk/>

Access past issues of Drug Safety Update at [www.mhra.gov.uk/mhra/drugsafety/update](http://www.mhra.gov.uk/mhra/drugsafety/update)

Recombinant human erythropoietins (r-HuEPOs) stimulate erythropoiesis. They are indicated for the treatment of symptomatic anaemia in patients with chronic kidney disease. Some r-HuEPOs are also authorised for the treatment of patients with non-myeloid cancer who develop symptomatic anaemia due to chemotherapy.

In December 2007, a Drug Safety Update article advised that r-HuEPOs should not be given to patients with cancer who do not fulfil the criteria in the authorised cancer indications, and that patients should be monitored closely to ensure that the lowest approved dose of r-HuEPO is used to adequately control of symptoms of anaemia. This advice was based mainly on data from five large controlled trials, which showed a consistent, unexplained statistically significant excess mortality in patients who had cancer-associated anaemia who received r-HuEPOs compared with controls. In these studies, r-HuEPOs had been given in a way that was not always consistent with prescribing recommendations: participants either did not have anaemia resulting from chemotherapy or haemoglobin was corrected to concentrations higher than 12 g/dL (7.5 mmol/L). Therefore, it was unclear what risks might apply to the use of r-HuEPOs to achieve haemoglobin concentrations lower than 12 g/dL (7.5 mmol/L) in patients with cancer who are receiving chemotherapy.

Further data have come to light for these medicines in cancer management.

### New data for r-HuEPOs in cancer

A prematurely terminated study<sup>1</sup> and an interim analysis from an unpublished study give further information on mortality and tumour progression in patients with cancer who receive r-HuEPOs.

#### *The Gynecologic Oncology Group study*

This study<sup>1</sup> compared the effect of maintaining haemoglobin concentration at 12 g/dL (7.5 mmol/L) or higher with r-HuEPO, with that of blood transfusion when haemoglobin concentration fell below 10 g/dL (6.2 mmol/L) on progression-free survival, overall survival, and local disease control in women who were receiving concurrent weekly cisplatin and radiotherapy for carcinoma of the cervix.

The study was terminated prematurely, with less than 25% of the planned number of patients (n=109), because of concerns about thromboembolic events in the r-HuEPO group. The r-HuEPO group were treated to maintain haemoglobin concentration between 12 g/dL (7.5 mmol/L) and 14 g/dL (8.7 mmol/L). 11 of 57 patients in this group had thromboembolism compared with four of 52 in the control group; none of the thromboembolic events was fatal. Median follow-up was 37 months (range

<sup>1</sup> Thomas G, et al. *Gynecol Oncol* 2008; 108: 317–25.

10–50). Progression-free survival at 3 years was lower in the r-HuEPO group than in the control group (58% vs 65%, respectively). Overall survival at 3 years was lower in the r-HuEPO group than in the control group (61% vs 75%, respectively).

#### *Unpublished study*

This study was a randomised, open-label trial in women with primary breast cancer who were randomly assigned one of two chemotherapy regimens for 24 weeks before surgery with or without radiotherapy. Patients in both treatment groups were also randomly allocated either darbepoetin alfa or no r-HuEPO. Darbepoetin alfa was given to maintain a haemoglobin concentration of 12 g/dL (7.5 mmol/L). Tumours were assessed every 12 weeks during chemotherapy, and follow-up was every 3 months for 2 years after the end of surgery or radiotherapy. 733 patients were analysed.

14% of patients who received darbepoetin alfa died compared with 10% of patients who received no r-HuEPO. Tumour progression was recorded for 25% of patients who received darbepoetin alfa compared with 19% of patients in the control group.

#### **Conclusions**

Neither study showed a statistically significant elevated risk associated with r-HuEPO treatment. However, their outcomes corroborate findings from previous studies of an increased risk of tumour progression and reduced overall survival associated with r-HuEPO in cancer settings. In the unpublished analysis, darbepoetin alfa was given in a way that resembles the authorised use for r-HuEPOs.

The risk of tumour progression associated with r-HuEPOs and their effect on overall survival in patients with cancer continue to be investigated. Further data should become available in due course, enabling further characterisation of the apparent risks.

**Has your  
colleague seen  
this bulletin?**

Further information is available from the European Medicines Agency at <http://www.emea.europa.eu/pdfs/human/press/pr/33396308en.pdf>. See also information for healthcare professionals at <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm>; click on July 2008

For NICE guidance on the use of these medicines in cancer, see <http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11990>

#### **Advice for healthcare professionals:**

- Available evidence suggests that use of r-HuEPOs in patients with cancer is associated with reduced overall survival and a negative effect on progression-free survival
- Data currently available do not allow definitive conclusion that the risk outweighs the benefit in their authorised indication in patients with cancer
- However, data do suggest that blood transfusion should be the preferred option for the management of anaemia in patients with cancer, particularly in those who are receiving adjuvant chemotherapy or who are being treated with curative intent
- Blood transfusion may also be preferable in patients with advanced or metastatic cancer who have a good survival prognosis
- The decision to administer r-HuEPOs should be based on an informed risk-benefit assessment with the participation of the patient, which takes into account: tumour type and stage; degree of anaemia; life-expectancy; the environment in which the patient is being treated; and the patient's preference

# Yellow Card Scheme update

The Yellow Card Scheme collects information on suspected adverse drug reactions in the UK. See [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)

For further information about black triangle drugs and vaccines, see Drug Safety Update July 2008, p 5. [www.mhra.gov.uk/mhra/drugsafetyupdate](http://www.mhra.gov.uk/mhra/drugsafetyupdate)

For further information and examples, see our website: <http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Medicines/Reportingsuspectedadversedrugreactions/Healthcareprofessionalreporting/Whattoreport/Seriousorsevere/index.htm>

## Serious versus severe reactions

Thank you for continuing to help us safeguard public health by sending us Yellow Cards of suspected adverse drug reactions. Please continue to report any suspected reaction to a black triangle (ie, new) drug or vaccine, and any serious suspected adverse reaction to an established drug or vaccine.

Although the safety profile of older drugs and vaccines has been established, previously unrecognised side-effects may be identified (particularly rare or delayed effects). Moreover, additional information about recognised side-effects associated with a medicine may help identify risk factors for a particular adverse reaction or ways in which a medicine can be used more safely.

### Serious reactions are those that are:

- Fatal
- Life-threatening
- Disabling or incapacitating
- The cause of admission to hospital or those that prolong hospital stay
- Congenital abnormalities
- Medically significant

The panel below lists some examples of serious reactions:

<b>Blood</b>	Coagulopathies; haemolytic anaemias
<b>Cardiovascular</b>	Arrhythmias; hypertension
<b>CNS</b>	Cerebrovascular accident; depression
<b>GI</b>	Liver cirrhosis; pancreatitis
<b>Immunological</b>	Anaphylaxis; vasculitis
<b>Malignancy</b>	Any
<b>Metabolic</b>	Diabetes; hyponatraemia
<b>Musculoskeletal</b>	Aseptic bone necrosis; pathological fracture
<b>Renal</b>	Renal failure; urinary retention
<b>Reproductive</b>	Congenital abnormalities; spontaneous abortion
<b>Respiratory</b>	Bronchospasm (including exacerbation); pneumonitis
<b>Skin</b>	Bullous eruptions; epidermal necrolysis
<b>Special senses</b>	Cataract

Please remember: we are interested to hear about any serious reaction for any drug or vaccine. You do not have to be sure about causality: if in doubt, please report.

### Severe reactions

By contrast with serious reactions, a severe reaction refers to the degree of harm, disability, or effect on quality of life. It might not be life-threatening or result in (or prolong) hospital admission. However, severe reactions can be an extreme experience for a patient. For example, a headache may be very severe, but would not usually be considered a serious adverse reaction. We are interested to receive reports of any suspected adverse reaction, irrespective of severity, for all black triangle drugs and vaccines.

# Hot topic

- Recent data for lenalidomide suggest potential for teratogenicity
- The Pregnancy Prevention Programme is vital for risk minimisation for women of childbearing potential
- Men must use condoms during lenalidomide or thalidomide treatment and for 1 week after dose interruption or cessation if their partner is pregnant or capable of becoming pregnant and is not using effective contraception
- Thalidomide and lenalidomide are associated with serious side-effects: neutropenia; thrombocytopenia; peripheral neuropathy (which may be permanent); venous thromboembolism; syncope and bradycardia; serious skin reactions, including Stevens-Johnson syndrome; and somnolence and dizziness

Access European Public Assessment Reports for lenalidomide and thalidomide, respectively, at:  
<http://www.emea.europa.eu/humandocs/PDFs/EPAR/revlimid/H-717-en6.pdf>

and  
<http://www.emea.europa.eu/humandocs/PDFs/EPAR/thalidomidepharmion/H-823-en6.pdf>

## Lenalidomide and thalidomide for multiple myeloma

Lenalidomide (Revlimid ▼) and thalidomide (Thalidomide Pharmion ▼) are licensed throughout the European Union for the management of multiple myeloma. Lenalidomide is authorised in combination with dexamethasone for treatment of multiple myeloma in patients who have received at least one previous treatment. Thalidomide is authorised in combination with melphalan and prednisone as first-line treatment for patients with untreated multiple myeloma who are age 65 years or older or who are not eligible for high-dose chemotherapy.

Lenalidomide and thalidomide are immunomodulatory agents. They have antineoplastic, antiangiogenic, and antierythropoietic properties.

### Lenalidomide

At the time of licensing in June 2007, it was assumed that lenalidomide would be a human teratogen because of its similarity to thalidomide. In rats, lenalidomide was not teratogenic at oral doses of up to 500 mg/kg a day. In rabbits, developmental toxicity was observed at the highest doses studied (10 mg/kg a day and 20 mg/kg a day). Furthermore, these doses were maternotoxic. The developmental toxicity observed in rabbits did not include limb abnormalities.

Recently, preliminary results have been obtained from a study of embryofetal development in primates. The study is not yet complete, but the currently available data show that offspring of monkeys that received lenalidomide during pregnancy had developmental anomalies typical of those associated with thalidomide (ie, short limbs; supernumerary or absent digits; and bent digits, wrist, or tail). A control group that received thalidomide in the same study had developmental anomalies similar to those seen with lenalidomide. No anomalies were observed in controls that received neither lenalidomide nor thalidomide in this study. These preliminary results provide the strongest evidence to date that lenalidomide is teratogenic in primates.

### Pregnancy Prevention Programme

Since licensing, risk-minimisation measures have aimed to prevent exposure of pregnant women to lenalidomide or thalidomide. Healthcare professionals and patients are required to adhere to the measures specified in the Pregnancy Prevention Programmes for these products. The Pregnancy Prevention Programmes link product supply to education of the prescriber, dispensing pharmacist, and patient. Where appropriate, the patient must present evidence of a recent negative pregnancy test before dispensing of the product.

Women of childbearing potential should use one effective method of contraception for at least 4 weeks before treatment, during treatment, during dose interruptions, and for 4 weeks after treatment has finished. Combined oral contraceptives are not recommended because of the increased risk of venous thromboembolism associated with multiple myeloma and with lenalidomide and thalidomide.

A pregnancy test must be done before start of treatment, monthly thereafter, and 4 weeks after the end of treatment. Pharmacists may not dispense more than 4 weeks' supply of lenalidomide or thalidomide for women of childbearing potential.

Pharmacies who wish to dispense thalidomide and lenalidomide must first register with the marketing authorisation holder. Registration aims to ensure that pharmacists have all the information necessary to implement the Pregnancy Prevention Programme.

For guidelines on conditions and restrictions to try to ensure safe and effective use of lenalidomide and thalidomide, respectively, see <http://www.emea.europa.eu/humandocs/PDFs/EPAR/revlimid/H-717-Annex-en.pdf> and <http://www.emea.europa.eu/humandocs/PDFs/EPAR/thalidomidepharmion/H-823-Annex-en.pdf>

A dedicated Prescription Authorisation Form must accompany every prescription for lenalidomide or thalidomide. This form documents that the patient has been appropriately counselled; that the prescriber and dispensing pharmacist have read and understood the educational material that applies to their role; that there has been a recent negative pregnancy test where appropriate; and that dispensing takes place within 7 days of the prescription date. There must be no more than 3 days between the dates of the last negative pregnancy test and the last prescription. Best practice is for the pregnancy test, prescribing, and dispensing to take place on the same day.

### Male patients

Thalidomide and lenalidomide appear in semen. Therefore, male patients must use condoms during treatment and for 1 week after dose interruption or cessation of treatment if their partner is pregnant or is capable of becoming pregnant and is not using effective contraception.

Pharmacists may not dispense more than 12 weeks' supply of lenalidomide or thalidomide for men (and for women who cannot become pregnant).

### Monitoring the effectiveness of the Pregnancy Prevention Programme

The MHRA monitors the effectiveness of risk-minimisation activities. The marketing authorisation holder will audit information recorded on Prescription Authorisation Forms—the success of which depends on the active participation of pharmacies registered to receive and supply thalidomide and lenalidomide. Pharmacists are urged to participate in this important data-gathering exercise. The information will help us identify at the earliest opportunity any weaknesses in the application of the Pregnancy Prevention Programme.

### Clinical safety

Thalidomide and lenalidomide are associated with other serious, or potentially serious, side-effects: neutropenia; thrombocytopenia; peripheral neuropathy (which may be permanent); venous thromboembolism; syncope and bradycardia; serious skin reactions, including Stevens-Johnson syndrome; and somnolence and dizziness.

Thalidomide was launched in June 2008, and to date we have received no spontaneous reports of adverse events. Lenalidomide has been available for prescription in the UK since June 2007. From June 2007 up to June 6, 2008, the MHRA has received five spontaneous reports in association with lenalidomide. Three reports had a fatal outcome—pulmonary oedema (1); stroke (1); and graft versus host disease (1). The two non-fatal reports involved abnormal liver function and bradycardia, respectively. There have been no reports involving exposure of unborn children to lenalidomide or thalidomide.

## Stop press

### Moxifloxacin: restricted use

Oral moxifloxacin (Avelox ▼, a fluoroquinolone antibiotic) is now restricted for use only when other medicines cannot be prescribed, or have failed, for treatment of acute bacterial sinusitis, acute exacerbation of chronic bronchitis, or community-acquired pneumonia. This restriction is based on evidence of an increased risk of life-threatening liver reactions and other serious risks associated with moxifloxacin.

Please prescribe oral moxifloxacin according to this updated information, while also considering official guidance on appropriate use of antibiotics and prevalence of resistance.

See  
<http://www.emea.europa.eu/pdfs/human/press/pr/38292708en.pdf/>

### Accusol 35 solutions: precipitate formation during haemofiltration

Accusol 35 solutions are indicated for treatment of acute and chronic renal failure as substitution solution in haemofiltration and haemodiafiltration, and as dialysis solution in haemodialysis and haemodiafiltration. We have been informed that some batches of Accusol 35 solution, Accusol 35 potassium 2 mmol/L, and Accusol 35 potassium 4 mmol/L have formed visible white precipitate during haemofiltration in continuous renal replacement therapy (CRRT, see image). The precipitate is calcium carbonate and has usually been seen in predilution or postdilution lines after several hours of therapy. The cause of the precipitate remains under investigation.

We advise in-use inspection of all batches of Accusol 35 licensed solutions.

#### Advice for healthcare professionals:

- Predilution and postdilution lines should be inspected at start of therapy and at least every 30 min during CRRT with Accusol 35 solutions
- If precipitate is observed, CRRT should be stopped and the blood returned to the patient using normal saline
- If a patient needs further CRRT, a new tubing set, haemofilter or dialyser, and Accusol 35 solution should be used before continuing
- CRRT may be continued using haemodialysis, if appropriate, as an alternative to haemofiltration or haemodiafiltration

For further information, see MHRA Drug Alert July 23, 2008:  
<http://www.mhra.gov.uk/Publications/Safetywarnings/Drugalerts/CON020742>

Example of white precipitate that might be seen in predilution or postdilution lines





## Caffeine for apnoea of prematurity: check dose regimen before use

For further information, refer to the Summary of Product Characteristics or Technical Prescribing Information for the product

Caffeine 5 mg/mL solution for injection is now available as a licenced medicine in the UK for intravenous or oral treatment of apnoea of prematurity.

The dose regimen of caffeine for the treatment of apnoea of prematurity is expressed differently depending on the salt. We are aware that different hospitals have been using unlicensed supplies of this medicine that have different product labelling—either caffeine 5 mg/mL or caffeine citrate 10 mg/mL. The two-fold difference in dose must be taken into account in prescribing and dispensing this medicine. Please ensure that you and your colleagues are fully familiar with this medicine and the appropriate dose regimen before use. The recommended doses are:

	Dose of caffeine 5 mg/mL solution for injection	Dose expressed as caffeine citrate*	Dose expressed as caffeine base*	Route	Frequency
Loading dose <sup>†</sup>	2 mL/kg	20 mg/kg	10 mg/kg	Intravenous infusion (over 30 min) or oral	Once <sup>†</sup>
Maintenance dose	0.5–1 mL/kg	5–10 mg/kg	2.5–5 mg/kg	Intravenous infusion (over 10 min) or oral	Every 24 hours (starting 24 hours after loading dose)

\* Note that dose expressed as caffeine base is half the dose expressed as caffeine citrate.  
<sup>†</sup> Caffeine is clinically effective within 4 hours. A second loading dose may be given if there is no response within this time. If there is no clinical response to the second loading dose, caffeine blood levels should be measured.

## Intrathecal drug pumps: risk of disrupted drug delivery

In April 2008, the MHRA placed on its website a field safety notice about the risk of discontinuation of drug delivery to patients with the Codman Archimedes intrathecal drug pump. Reports have shown that the flow of drug either slows down considerably or stops completely in a short timeframe after implantation (ie, after the first 6–12 weeks). Cessation of drug delivery may result in the return of pain in patients who are receiving intrathecal morphine; the return of spasticity in patients who are receiving intrathecal baclofen; or in other symptoms of drug withdrawal. The risk seems to be associated with low-flow-rate models. Codman has ceased supply of all 0.5 mL, 0.8 mL, and 1.0 mL (per 24 h) flow-rate models and recalled all unimplanted units, pending further investigation.

### Advice for healthcare professionals:

- Please ensure that unimplanted units have been returned to Codman
- For patients with these implants, consider more frequent follow-up in the first 12 weeks after implantation, when risk of pump failure is highest
- Ensure that only approved drugs and correct formulations are used in these pumps; off-label formulations can damage the flow-restrictor chip

See <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/FieldSafetyNoticesformedicaldevices/CON015447>

## Metronidazole for *Clostridium-difficile*-associated diarrhoea: use oral formulation

The National Patient Safety Agency has received five reports of erroneous prescribing of intravenous metronidazole, rather than the oral formulation, for the treatment of *Clostridium-difficile*-associated diarrhoea (CDAD). Only the oral formulation of metronidazole should be used for this indication, unless advised otherwise (in exceptional cases) by specialists in the treatment of CDAD.

NPSA website: <http://www.npsa.nhs.uk/>

## Other information from the MHRA

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### Patient Information Leaflet of the month: AmBisome

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 **AmBisome** (liposomal amphotericin), an intravenous infusion for fungal infections and visceral leishmaniasis.

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)

### Review of unlicensed medicines

We are currently reviewing the regulatory arrangements in the UK that allow an authorised healthcare professional to commission an unlicensed medicine to the special needs of a particular patient. An informal consultation period ended on June 30, 2008. After informal meetings with a range of stakeholders, a formal consultation exercise is likely to follow that will outline specific proposals for reform of the current arrangements. You can stay up to date on this topic via our website.

For further information, see  
<http://www.mhra.gov.uk/Howweregulate/Medicines/Reviewofunlicensedmedicines/CON018138>

### Advertising complaints

We scrutinise the advertising of licensed medicines and investigate complaints we receive. The outcomes of our investigations are published regularly on our website, which supplements other actions that may be taken to alert healthcare professionals and the public about misleading advertising (eg, publication of a corrective statement).

Please tell us about any advertising that concerns you. Advertising can appear: in medical journals, newspapers, magazines; on television or the internet; or in contact with pharmaceutical company representatives.

Read about the outcomes of recent advertising investigations at  
<http://www.mhra.gov.uk/Howweregulate/Medicines/Advertisingofmedicines/Advertisinginvestigations/index.htm>;  
for more information about how to complain about potentially misleading advertising see  
<http://www.mhra.gov.uk/Howweregulate/Medicines/Advertisingofmedicines/Advertisinginvestigations/Advertisingcomplaintform/index.htm>

### Public consultation: supply and administration of medicines by the armed forces

We have launched a consultation to seek views on proposals to allow members of the armed forces to supply and administer medicines in emergencies or in circumstances where medical support may not be available (eg, isolated location). Responses to the consultation are welcome by Sept 24, 2008.

To read more about the consultation and to respond, see  
<http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MXs/CON020528>

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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Report a suspected adverse drug reaction at <http://www.yellowcard.gov.uk>