

# 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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The final issue of *Drug Safety Update* for 2007 has some important information for healthcare professionals. There is new prescribing advice for use of recombinant human erythropoietin in light of new evidence that affects the balance of risks and benefits (page 2). And please see page 5 for further information on the continuing assessment of the safety of glitazones for treatment of type 2 diabetes.

Moreover, we wish to draw your attention to new measures that have been introduced to help minimise the risk of fatal overdose associated with the anti-depressant dosulepin, including changes to pack sizes and their design (page 7).

Healthcare professionals who specialise in obstetrics may take particular interest in our drug safety advice articles on the risk of ACE inhibitors and angiotensin II receptor antagonists in pregnancy (page 8) and on the risk of myocardial ischaemia associated with short-acting  $\beta$  agonists, which includes advice on the use of this drug class in the management of premature labour (page 8).

Finally, why not try our end-of-year quiz to test your knowledge of recent drug-safety information that we have published in the bulletin (page 14, answers on page 17)? Please do not send your answers to us—it's just for fun! May I take this opportunity to wish you a very happy festive break, and a healthy and successful 2008.

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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

## Recombinant human erythropoietins: new prescribing advice

**Keywords:** Recombinant human erythropoietins, epoetin, erythropoiesis, renal failure, chronic kidney disease, cancer, anaemia, haemoglobin concentration, cardiovascular events, thrombosis, tumour progression, survival

**Overcorrection of haemoglobin concentration in patients with chronic kidney disease may increase the risk of death and serious cardiovascular events, and in patients with cancer may increase the risk of thrombosis and related complications. Recombinant human erythropoietins should not be given to patients with cancer who do not fulfil the criteria in the authorised cancer indications**

Recombinant human erythropoietins (r-HuEPOs) stimulate erythropoiesis. They are indicated for the treatment of anaemia in patients with chronic kidney disease. Some r-HuEPOs are also authorised for the treatment of patients with non-myeloid cancer who develop anaemia after chemotherapy. Five r-HuEPOs are authorised in the UK: epoetin alfa (Eprex); darbepoetin alfa (Aranesp, a hyper-glycosylated epoetin derivative); epoetin beta (NeoRecormon); epoetin delta (Dynepo▼); and methoxy polyethylene glycol-epoetin beta (Mircera▼). Biosimilar analogues of epoetin alfa have also been granted Marketing Authorisations.

The safety of r-HuEPOs has been reviewed because recently published data from clinical trials have shown a consistent, unexplained statistically significant excess mortality in patients with anaemia associated with cancer who have been treated with r-HuEPOs. Furthermore, results of studies suggest that treatment of anaemia with r-HuEPOs in patients with chronic kidney disease to achieve relatively high target haemoglobin concentrations may be associated with increased risk of mortality and cardiovascular morbidity.

### Patients with cancer: risk of tumour progression and reduced overall survival

Five large controlled trials (including two unpublished studies) have assessed survival and tumour progression<sup>1-3</sup> in a total of 2833 patients (see **table**). Two studies recruited patients who were receiving chemotherapy. Target haemoglobin concentration in two studies was more than 13 g/dL; in the remaining three studies it was 12–14 g/dL. The open-label study recorded no difference in overall survival between patients given r-HuEPOs and controls. In the four placebo-controlled studies, the hazard ratios for overall survival ranged from 1.25 to 2.47 in favour of controls. These studies have shown a consistent, unexplained statistically significant excess mortality in patients who have anaemia associated with various common cancers who received r-HuEPOs, compared with controls. Differences in overall survival in the trials could not be explained satisfactorily by differences in the incidence of thrombosis and related complications between the r-HuEPO groups and the control groups.

The extent to which these outcomes might apply to the use of r-HuEPOs to achieve haemoglobin concentrations lower than 12 g/dL in patients with cancer who are receiving chemotherapy is unclear because few such patients were included in the data reviewed.

Access a public statement from the European Medicines Agency on the conclusions and recommendations of the safety review of these medicines at <http://www.emea.europa.eu/pdfs/human/press/pus/49618807en.pdf>

A Public Assessment Report that summarises the latest evidence for the safety of r-HuEPOs in patients with cancer is available on our website at [http://www.mhra.gov.uk/home/idcplg?ldcService=SS\\_GET\\_PAGE&useSecondary=true&ssDocName=CON2033006&ssTargetNodeId=221](http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2033006&ssTargetNodeId=221)

- 1 Henke M, et al. *Lancet* 2003; **362**: 1255–60.
- 2 Leyland-Jones B, et al. *J Clin Oncol* 2005; **23**: 5960–72.
- 3 Wright JR, et al. *J Clin Oncol* 2007; **25**: 1027–32.

Study (number of patients)	Treatment	Design	Cancer type	Hazard ratio (95% CI)	
				Overall survival	Tumour progression
Henke et al <sup>1</sup> (n=351)	Epoetin beta	Double-blind, placebo-controlled	Squamous cancer of head and neck (patients given radiotherapy)	1.39 (1.05–1.84)	1.69 (1.16–2.47)
DAHANCA 10 (n=484)	Darbepoetin alfa	Open-label; control group received radiotherapy alone	Squamous cancer of head and neck (patients given radiotherapy)	No difference	1.1; p=0.01
20010103 (n=989)	Darbepoetin alfa	Double-blind, placebo-controlled	Various solid tumours (patients did not receive radiotherapy or chemotherapy)	1.25 (1.04–1.51)	Not available
Leyland-Jones et al <sup>2</sup> (n=939)	Epoetin alfa	Double-blind, placebo-controlled	Metastatic breast cancer (patients given radiotherapy or chemotherapy)	1.36 (1.05–1.75)	No difference
Wright et al <sup>3</sup> (n=70)	Epoetin alfa	Double-blind, placebo-controlled	Non-small-cell lung cancer (patients given non-platinum chemotherapy)	2.47 (1.05–5.83)	Not available

Table: Summary of clinical trials of r-HuEPOs in cancer setting

A summary of study 20010103 is available as an abstract to an oral presentation by J Glaspy and colleagues given at the 2007 annual meeting of the American Association for Cancer Research, Los Angeles, CA, USA; April 14-18, 2007. See <http://www.abstractsonline.com/viewer/?mkey=%7BE3F4019C%2D0A43%2D4514%2D8F66%2DB86DC90CD935%7D>

A systematic review has analysed more than 9000 patients with cancer from 57 clinical trials.<sup>4</sup> Meta-analysis of overall survival showed a hazard ratio of 1.08 in favour of controls (95% CI 0.99–1.18; 42 trials, 8167 patients). Patients assigned r-HuEPOs had an increased relative risk of thromboembolic events compared with controls (1.67 [95% CI 1.35–2.06]; 35 trials, 6769 patients).

4 Bohlius J, et al. *Cochrane Database of Systematic Reviews* 2006; **3**: CD003407 (DOI:10.1002/14651858.CD003407.pub4).

The available data do not enable accurate definition of a target range for haemoglobin concentration that has a consistently favourable balance of risks and benefits. However, no advantage has been shown for a haemoglobin concentration higher than 12 g/dL in patients with cancer. The purpose of r-HuEPO treatment is to relieve symptoms of anaemia and avoid the need for blood transfusion. Treatment should stop when symptoms of anaemia have been adequately controlled. Symptoms of anaemia may be controlled in some patients at haemoglobin concentrations lower than those conventionally considered to be normal.

There is currently no evidence to suggest that r-HuEPOs may adversely affect the risk of tumour progression and overall survival in patients with cancer who meet the criteria in the authorised cancer indications. The safety of r-HuEPOs will be reassessed when additional data in this patient population become available.

A Public Assessment Report that summarises the latest evidence for the safety of r-HuEPOs in patients with chronic kidney disease is available on our website at [http://www.mhra.gov.uk/home/idcplg?ldcService=SS\\_GET\\_PAGE&useSecondary=true&ssDocName=CON2033006&ssTargetNodeid=221](http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2033006&ssTargetNodeid=221)

5 Ajay K, et al. *N Engl J Med* 2006; **355**: 2085–98.

6 Tilman B, et al. *N Engl J Med* 2006; **355**: 2071–84.

7 Phrommintikul A, et al. *Lancet* 2007; **369**: 381–88.

## Patients with chronic kidney disease: risk of mortality and cardiovascular morbidity

Two studies<sup>5,6</sup> have compared cardiovascular outcomes in patients with chronic kidney disease who were treated with r-HuEPOs to achieve either a high or low haemoglobin concentration. One study<sup>5</sup> showed that patients who were given epoetin alfa to achieve a haemoglobin concentration of 11·3 g/dL had a significantly longer time to the composite endpoint of death, myocardial infarction, hospitalisation for congestive heart failure (excluding renal-replacement therapy), or stroke than did those treated to achieve a haemoglobin concentration of 13·5 g/dL.

The second study<sup>6</sup> compared cardiovascular outcomes in patients with chronic kidney disease and anaemia who were treated with epoetin beta to achieve a haemoglobin concentration of either 10·5–11·5 g/dL or 13–15 g/dL. These groups did not differ significantly in frequency of death from cardiovascular causes, or in time to death from cardiovascular causes or all causes. Trends for all-cause mortality and cardiovascular morbidity consistently favoured the low-target-haemoglobin group, but differences between groups were small. Groups did not differ in the frequency of thrombotic complications.

Both studies<sup>5,6</sup> showed no benefit associated with correction of haemoglobin concentration to high levels compared with low levels. Assuming either the same cardiovascular risk for both treatment strategies, or a slightly lower risk with low target haemoglobin as suggested by the outcome of the first study,<sup>5</sup> and given the small trends in the second study,<sup>6</sup> there can be little justification for the correction of haemoglobin concentration beyond the minimum level that is compatible with good control of symptoms of anaemia in patients with chronic kidney disease.

A meta-analysis of nine prospective randomised controlled trials<sup>7</sup> assessed all-cause mortality and cardiovascular events associated with r-HuEPO treatment to achieve different ranges of haemoglobin concentration in patients with anaemia due to chronic kidney disease. The results suggest an increased risk of all-cause mortality in patients with anaemia who are treated with r-HuEPOs to achieve a haemoglobin concentration between 12 g/dL and 16 g/dL compared with those treated to achieve a haemoglobin concentration less than 12 g/dL. The best estimate of relative risk of death associated with higher target haemoglobin concentrations was 1·17. No clinical benefit was identified with attaining a haemoglobin concentration higher than 12 g/dL that could not be gained at lower haemoglobin concentrations in patients with chronic kidney disease.

### Information and advice for healthcare professionals:

- The authorised indication for patients with chronic kidney disease has been changed to stipulate treatment with r-HuEPOs only if symptoms of anaemia are present. All other authorised indications remain unchanged
- Dose recommendations have been changed, where necessary, to stipulate a uniform target haemoglobin concentration range of 10–12 g/dL (6·2–7·5 mmol/L). Haemoglobin concentrations higher than 12 g/dL (7·5 mmol/L) should be avoided

- Guidance has been provided in the prescribing information for every r-HuEPO for appropriate dose adjustment to maintain haemoglobin concentration within the recommended range
- Patients should be monitored closely to ensure that the lowest approved dose of r-HuEPO is used to provide adequate control of the symptoms of anaemia

Prescribing information for r-HuEPOs has been/is being revised to emphasise that treatment to achieve haemoglobin concentrations higher than 12 g/dL (7.5 mmol/L) might increase the risk of death and serious cardiovascular events. Information has also been added about the risk of reduced overall survival and shortened time to tumour progression in patients with cancer who have been treated with r-HuEPOs to achieve haemoglobin concentrations higher than those recommended, and/or to treat patients with anaemia who have not received chemotherapy.

## Rosiglitazone and pioglitazone: cardiovascular safety

**Keywords:** rosiglitazone, pioglitazone, thiazolidinediones, type 2 diabetes, cardiovascular, cardiac ischaemia, insulin, fluid retention, risk-benefit

**Rosiglitazone and pioglitazone should not be used in people with heart failure or history of heart failure; incidence of heart failure is increased when rosiglitazone or pioglitazone are combined with insulin. Closely monitor patients during treatment for signs and symptoms of fluid retention, including weight gain or oedema. Rosiglitazone might be associated with a small increased risk of cardiac ischaemia, particularly in combination with insulin; rosiglitazone should be used in patients with previous or current ischaemic heart disease only after careful evaluation of individual risk**

Rosiglitazone (Avandia, Avandamet▼) and pioglitazone (Actos, Competact▼) are treatments for patients with type 2 (ie, non-insulin-dependent) diabetes and belong to a class of drugs called thiazolidinediones (also called glitazones).

Concerns have arisen about the cardiovascular safety of thiazolidinediones: heart failure is a recognised risk, and more recently analyses<sup>1</sup> have suggested that rosiglitazone might be associated with a small increased risk of myocardial infarction. These concerns have led to a Europe-wide review of available data for the safety and efficacy of thiazolidinediones, including cardiovascular safety.

Revised prescribing information emphasises that the benefits of rosiglitazone and pioglitazone for treatment of type 2 diabetes continue to outweigh the risks. However, the prescribing information will be updated to include a warning that rosiglitazone should be used in patients with ischaemic heart disease only after careful evaluation of every patient's individual risk. Furthermore, rosiglitazone combined with insulin should be used only in exceptional cases and under close supervision.

See *Drug Safety Update* 2007; **1**(3): 10;  
[www.mhra.gov.uk/mhra/drugsafetyupdate](http://www.mhra.gov.uk/mhra/drugsafetyupdate)

<sup>1</sup> Nissen SE and Wolski K. *N Engl J Med* 2007; **256**: 1–15.

Access further information from the European Medicines Agency at:  
<http://www.emea.europa.eu/pdfs/human/press/pr/48427707en.pdf>

Access a summary of data for the safety of glitazones at [http://www.mhra.gov.uk/home/idcplg?ldcService=SS\\_GET\\_PAGE&nodeId=223](http://www.mhra.gov.uk/home/idcplg?ldcService=SS_GET_PAGE&nodeId=223)

### Fluid retention and cardiac failure

Rosiglitazone and pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. Patients at particular risk are: those who receive concurrent insulin or sulphonylurea; those at risk of heart failure (eg, previous myocardial infarction or symptomatic coronary artery disease); and those with reduced cardiac reserve.

#### Advice for healthcare professionals:

- Rosiglitazone and pioglitazone should not be used in people with heart failure or history of heart failure (ie, New York Heart Association class I–IV)
- Incidence of heart failure is increased when rosiglitazone or pioglitazone is combined with insulin
- People who are at particular risk of heart failure should start rosiglitazone or pioglitazone at the lowest available dose; any dose increase should be done gradually
- Patients should be monitored closely during treatment for signs and symptoms of fluid retention, including weight gain or oedema
- Treatment should be stopped if any deterioration in cardiac status occurs

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

2 Lincoff MA, et al. *JAMA*; 2007; **298**: 1180–88.

3 See <http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4308s1-03-gsk-steward.pdf>

4 Koro CE, et al. *Diabetes* 2004; **53** (supl 2): A247.

### Myocardial ischaemia

A meta-analysis of data from clinical trials showed that the overall incidence of cardiac ischaemic events was higher for rosiglitazone than for comparators (1.99% vs 1.51%; hazard ratio 1.31 [95% CI 1.01–1.70]); however, there was no increase in overall mortality (see Summary of Product Characteristics for Avandia). The risk of cardiac ischaemic events seems to be particularly marked when rosiglitazone is combined with insulin, or in patients with a previous or current ischaemic heart disease. Analysis of pioglitazone trials did not suggest an increased risk of cardiac ischaemia<sup>2</sup>. However, comparative data do not provide good evidence of a difference between rosiglitazone and pioglitazone for risk of cardiac ischaemia events<sup>3,4</sup>. Further studies are under way and advice will be updated as new data become available.

#### Advice for healthcare professionals:

- Rosiglitazone might be associated with a small increased risk of cardiac ischaemia
- Clinical trials have recorded an increased risk of cardiac ischaemia for rosiglitazone combined with insulin. Therefore, this combination should be used only in exceptional circumstances and under close supervision
- Rosiglitazone should be used in patients with previous or current ischaemic heart disease only after careful evaluation of their individual risk

## Dosulepin: measures to reduce risk of fatal overdose

**Keywords:** dosulepin, dothiepin, tricyclic antidepressants, overdose

**Dosulepin has a small margin of safety between the (maximum) therapeutic dose and potentially fatal doses. Use in new patients should be avoided; where necessary, only specialist-care prescribers should start treatment for patients who have not previously received dosulepin, and prescribers should limit the amount issued per prescription. To reduce the risk of fatal overdose, dosulepin has been available only in child-resistant blister packs since November 2007**

Dosulepin (previous BAN dothiepin) is a tricyclic antidepressant, used especially where an anti-anxiety effect is required. It is available as 25-mg capsules and 75-mg tablets.

Because of the narrow safety margin of dosulepin, the clinical guideline on depression management<sup>1</sup> developed by the National Institute for Health and Clinical Excellence in conjunction with the National Collaborating Centre for Mental Health recommends that dosulepin is a less-appropriate treatment for depression and that only specialists or GPs with a special interest in psychiatry should prescribe it.

Nevertheless, dosulepin continues to be prescribed widely: it accounts for about 10% of the antidepressant market in England; more than 200 000 adults in the UK received a prescription for it in the 12 months to June 2006; and most prescriptions for adults contain 56 tablets or capsules (ie, 1–2 months' supply).

Every year, up to 200 people in England and Wales commit suicide or fatally overdose with dosulepin.<sup>2–4</sup> About 20% of fatal dosulepin overdoses are associated with accidental death.<sup>5</sup> Doses of 750 mg in adults and 15 mg/kg in children have been associated with fatalities.<sup>6</sup>

The Commission on Human Medicines has considered the evidence and advised that the safety concerns due to toxicity of dosulepin in overdose are sufficient to warrant discouraging of its use for new patients and for introduction of risk-minimisation measures.

Since November 2007, pack sizes have been limited and the packaging made safer to limit the potential for fatal overdose with products that contain dosulepin. These measures include:

- Introduction of smaller blister packs, equivalent to 2 weeks' supply of 75 mg per day
- Maximum pack sizes equivalent to 4 weeks' supply of 25 mg per day or 75 mg per day
- Introduction of child-resistant blister packs

1 NICE clinical guideline 23 (2004). Depression: management of depression in primary and secondary care. See <http://www.nice.org.uk/guidance/index.jsp?action=download&o=29605>

Data are derived from the Prescription Pricing Authority and IMS Health databases

2 Office for National Statistics report. Deaths related to drug poisoning: England and Wales, 1998–2002. *Health Stat Q* 2004; **21**: 59–66.

3 Buckley NA, McManus PR. *BMJ* 2002; **325**: 1332–33.

4 Morgan O, et al. *Health Stat Q* 2004; **23**: 18–24.

5 Cheeta S, et al. *Br J Psychiatry* 2004; **184**: 41–47.

6 National Poisons Information Service. Dothiepin monograph (UK PID) 1998. See <http://www.intox.org/databank/documents/pharm/dothiepn/ukpid22.htm>

Examples of medicines that should be avoided during dosulepin use are: alcohol; general anaesthetics; opioid analgesics; anti-arrhythmics; moxifloxacin; SSRIs; MAOIs; sedating antihistamines; antipsychotics; anxiolytics; hypnotics; atomoxetine; diltiazem; verapamil; disulfiram; dopaminergics; lithium; pentamidine isethionate; sibutramine; and sympathomimetics.

#### Advice for healthcare professionals:

- Initiation of treatment for patients who have not previously received dosulepin should be restricted to specialist-care prescribers
- A limited number of tablets should be prescribed to reduce the risk of overdose for all patients, especially those at risk of suicide
- A maximum prescription equivalent to 2 weeks' supply of 75 mg per day should be considered in patients with increased risk factors for suicide at initiation of treatment, during any dose adjustment, and until improvement occurs
- Concomitant medicines that may increase the risk of toxicity associated with dosulepin should be avoided
- There is no immediate need to change treatment for established patients
- Patients should be advised to store tablets securely, out of sight and reach of children
- In cases of overdose, patients should seek immediate medical attention

At present, the MHRA is reviewing whether risk-minimisation measures are appropriate for other tricyclic antidepressants, and further advice will be issued.

## ACE inhibitors and angiotensin II receptor antagonists: not for use in pregnancy

**Keywords:** Hypertension, pregnancy, ACE inhibitor, angiotensin II receptor antagonists, congenital anomaly, teratogenicity, diabetes

**ACE inhibitors and angiotensin II receptor antagonists should not be used at any stage of pregnancy. Use in women who are planning pregnancy should be avoided unless absolutely necessary, in which case the potential risks and benefits should be discussed**

See individual Summaries of Product Characteristics at the Electronic Medicines Compendium  
<http://emc.medicines.org.uk>

Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists are licensed for various indications, including hypertension, and may be particularly suitable for young patients with high blood pressure (but not those of black ethnic origin) and those with some comorbidities such as diabetic nephropathy.

Angiotensin II is essential for normal kidney development, and use of ACE inhibitors and angiotensin II receptor antagonists in late pregnancy has been associated with renal dysfunction, oligohydramnios, neonatal anuria, and other congenital anomalies such as skull ossification defects. However, data have also suggested an increased risk of congenital anomaly after exposure limited to the first trimester of pregnancy.

1 Cooper WO, et al. *N Engl J Med* 2006; **354**: 2443–51.

A US cohort study<sup>1</sup> that used Medicaid data from Tennessee noted an increased risk of congenital anomalies with ACE inhibitors, particularly anomalies of the cardiovascular system and CNS. On the basis of 18 cases (all major anomalies) among 209 infants exposed to ACE inhibitors in the first trimester, the table shows adjusted risk ratios for congenital anomalies compared with infants who had no exposure to antihypertensive medicines in the first trimester:

	Risk ratio (95% CI)
<b>ACE inhibitor exposure</b>	
Any major congenital malformation	2.71 (1.72–4.27)
Cardiovascular malformation	3.72 (1.89–7.30)
CNS malformation	4.39 (1.37–14.02)
<b>Other antihypertensive exposure*</b>	
Major congenital malformation	0.66 (0.25–1.75)

Table: **Adjusted risks for exposure to ACE inhibitor or other antihypertensive versus no antihypertensive in first trimester<sup>1</sup>**

\*Angiotensin II receptor antagonists were excluded.

The table also shows that this study<sup>1</sup> identified no increased risk with other classes of antihypertensives; however, angiotensin II receptor antagonists were excluded.

Because maternal diabetes is independently associated with an increased risk of congenital anomaly, the researchers attempted to exclude mothers with known diabetes. Although the study<sup>1</sup> has some limitations, such as a small number of events, it raises substantial concern about possible teratogenicity with ACE inhibitors in the first trimester of pregnancy.

There are fewer data for the risks with angiotensin II receptor antagonists, although there are case reports<sup>2,3</sup> of congenital anomaly after exposure to these agents during the second and third trimesters. Furthermore, there are no data to exclude a possible risk similar to that noted for ACE inhibitors in the first trimester.

2 Velázquez-Armenta EY, et al. *Hypertens Pregnancy* 2007; **26**: 51–66.

3 Saji H, et al. *Lancet* 2001; **357**: 363.

**Advice for healthcare professionals:**

**Patients who are planning pregnancy:**

- Unless continued treatment with an ACE inhibitor or angiotensin II receptor antagonist is considered essential (eg, in some patients with hypertension and diabetic nephropathy), women who are planning pregnancy should be switched to alternative antihypertensive treatments that have an established safety profile for use in pregnancy
- The balance of risks and benefits of continued treatment with an ACE inhibitor or angiotensin II receptor antagonist versus the potential risk of congenital anomaly should be discussed with the patient

**Patients who are pregnant:**

- On diagnosis of pregnancy, treatment with an ACE inhibitor or angiotensin II receptor antagonist should be stopped as soon as possible, and, if appropriate, alternative treatment should be started

## Short-acting $\beta$ agonists: myocardial ischaemia

**Keywords:** myocardial ischaemia, tocolysis, premature labour, beta agonist,  $\beta$  agonist, cardiovascular, salbutamol, terbutaline, bambuterol, fenoterol, ritodrine, ephedrine, orciprenaline

**Myocardial ischaemia may occur with use of short-acting  $\beta$  agonists: patients with pre-existing ischaemic heart disease or risk factors for cardiovascular disease should not be given short-acting  $\beta$  agonists for management of premature labour, and should be alert to symptoms of worsening heart disease if receiving treatment for respiratory disease**

Short-acting  $\beta$  agonists are indicated for reversible airway obstruction, or prevention of premature labour, or both. Short-acting  $\beta$  agonists are available as inhalation, oral, intravenous, or subcutaneous preparations.

Cardiovascular effects might occur with any sympathomimetic drug, including short-acting  $\beta$  agonists. There is some evidence from post-marketing data and published literature<sup>1-4</sup> of myocardial ischaemia associated with use of short-acting  $\beta$  agonists.

- 1 Kochiadakis GE, et al. *Int J Cardiol* 2007; **117**: 408-10.
- 2 Salpeter SR, et al. *Chest* 2004; **125**: 2309-21.
- 3 Pincus R. *Aust N Z J Obstet Gynaecol* 1981; **21**: 1-4.
- 4 James AH, et al. *Circulation* 2006; **113**: 1564-71.

### Obstetric use

In women with significant risk factors for, or women who have pre-existing, ischaemic heart disease the risk of myocardial ischaemia outweighs the benefits of use of short-acting  $\beta$  agonists such as ritodrine, salbutamol, or terbutaline for the prevention of premature labour. Other treatments (eg, atosiban) do not carry a similar risk.

In all other patients, short-acting  $\beta$  agonists should be used with caution in the prevention of premature labour because of the risk of myocardial ischaemia. Attention should be given to fluid balance and monitoring of cardiorespiratory function (ECG monitoring should be considered). Discontinue treatment if signs of myocardial ischaemia develop during treatment with short-acting  $\beta$  agonists.

### Respiratory use

Patients with a history of heart disease, including angina or rhythm disturbance, should be advised to continue treatment with short-acting  $\beta$  agonists, but to seek medical advice if symptoms such as shortness of breath or chest pain occur during treatment because they may suggest worsening heart disease.

## Yellow Card scheme update

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

In October, 2002, the MHRA launched the electronic Yellow Card—a method of reporting via the internet adverse drug reactions that complements paper-based, traditional Yellow Cards. You can access the electronic Yellow Card by visiting [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)

We have received more than 4000 electronic Yellow Cards since its launch. For January–August 2007, 10% of reports sent by healthcare professionals were electronic; 29% of patient reports were received by this route.

### **Have you considered reporting a suspected adverse drug reaction to us via an electronic Yellow Card?**

The electronic Yellow Card plays a vital part in the MHRA's timely identification of drug-safety signals and subsequent activities to ensure that the benefits of a medicine outweigh the potential risks. Electronic reports will reach us more quickly than paper Yellow Cards, enabling us to take swifter action if necessary.

Electronic reporting will soon be getting easier. As part of a wider strategy to strengthen reporting to the Yellow Card scheme, we have listened to feedback received from those who use the electronic Yellow Card, and we have developed an improved electronic reporting form. For instance, users will have the option to register their details so that they no longer have to complete this information every time they send a report.

Pharmacists had the opportunity to view and comment on early screen prototypes of the enhanced electronic Yellow Card at this year's British Pharmaceutical Conference in September. We hope to launch the new electronic Yellow Card on the MHRA's website in spring 2008; we will keep you updated about the launch date and we will be inviting you to give your views. In the meantime, you can continue to report electronically via the current form at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)

# Hot topics

## Varenicline: possible effects on driving; psychiatric illness

Varenicline (Champix▼) is an aid to smoking cessation; it was launched in the UK in December, 2006. Varenicline is a partial agonist at the nicotinic  $\alpha 4\beta 2$  receptor.

15 000–20 000 patients have used varenicline since its launch. Up to 26 September, 2007 the MHRA had received 839 reports of suspected adverse drug reactions in relation to the use of varenicline. Most of these reports were of well-recognised adverse drug reactions for this medicine, such as:

• Abnormal dreams	52
• Dizziness	49
• Fatigue	37
• Headache	82
• Insomnia	34
• Nausea	183
• Somnolence	21
• Vomiting	67

### Possible effects on driving

Healthcare professionals and patients should be aware of the possible effects of varenicline on driving. The Summary of Product Characteristics (SPC) advises that patients should not drive until they know whether varenicline affects their driving ability; a similar warning is in the Patient Information Leaflet.

### Psychiatric illness

The MHRA has received 46 reports of depression associated with the use of varenicline, generally in patients with a previous psychiatric history, and 16 reports of suicidal ideation. The MHRA is monitoring closely the issue of suicidality in patients taking varenicline. Of note: stopping smoking—with or without medication—may exacerbate an underlying psychiatric condition. The SPC for varenicline advises particular care in patients with a previous history of psychiatric illness, and states that patients should be advised accordingly.

### Effects on drug metabolism

Healthcare professionals should be aware that stopping smoking—with or without medication—may affect the metabolism of some drugs, for which dose adjustment may be essential (eg, insulin, theophylline, and warfarin).

As with all black triangle drugs (▼), please continue to report to us via the Yellow Card scheme all reactions which you suspect may be related to the use of varenicline—including any considered not to be serious and reactions that are well-recognised. You do not have to be certain about causality: if in doubt, please report.

For further general information about smoking-cessation aids, see [http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PA GE&nodeId=1095](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PA GE&nodeId=1095)

You can complete a Yellow Card online, or find out more about the scheme, at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk) see also page 11.

**The ideal anti-inflammatory prescribing choice will vary between patients, depending on individual risk factors, therapeutic response, and patient preference. Patients should use the lowest effective dose, and the shortest duration of treatment necessary to control symptoms**

To access the NPC's advice, see a recent MeReC Extra, which is available at <http://www.npc.co.uk/>. The NPC has also recently produced a range of additional materials in its virtual e-Learning 'building' <http://www.npci.org.uk/>. Click on the lift in reception, then select Musculoskeletal Pain floor from the options in the Pain Management floors.

Access the Commission's advice at [http://www.mhra.gov.uk/home/idcplg?1dcService=SS\\_GET\\_PAGE&nodeId=227](http://www.mhra.gov.uk/home/idcplg?1dcService=SS_GET_PAGE&nodeId=227)

- 1 *Current Problems in Pharmacovigilance* April 2002; **28**: 5.
- 2 *Drug Safety Update* 2007; **1** (3): 2–4.
- 3 Laine L, et al. *Lancet* 2007; **369**: 465–73.
- 4 Ray WA, et al. *Gastroenterology* 2007; **133**: 790–98.

## NSAIDs and coxibs: balancing of cardiovascular and gastrointestinal risks

Gastrointestinal toxicity and cardiovascular toxicity are the two most important safety concerns for non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors (coxibs). Clinical trial and epidemiological data have given important information on the level of risk with individual medicines. However, these data are complex and there are no robust comparisons for many NSAIDs. Most evidence relates to the coxibs, naproxen, ibuprofen, and diclofenac.

The National Prescribing Centre (NPC) has summarised up-to-date prescribing advice and information in relation to NSAIDs, which is available through their website.

### Thrombotic risks

In October 2006, the Commission on Human Medicines (CHM) gave advice on the latest evidence for cardiovascular thrombotic risks:

- Diclofenac 150 mg daily has a thrombotic risk profile similar to that of at least one coxib (etoricoxib) and possibly others
- Naproxen 1000 mg daily has a lower thrombotic risk than coxibs and, overall, epidemiological data do not suggest an increased risk of myocardial infarction
- For ibuprofen at high doses (eg, 2400 mg daily) there may be a small thrombotic risk, but at lower doses (eg, 1200 mg daily or less) epidemiological data do not suggest an increased risk of myocardial infarction

Less evidence is available for other NSAIDs, but they may be associated with a small risk of thrombotic events, especially with long duration of treatment and high doses.

### Gastrointestinal risks

The Committee on Safety of Medicines (now the Commission on Human Medicines) has reviewed the relative gastrointestinal risks of NSAIDs on several occasions.<sup>1</sup> Recently, we have highlighted the high gastrointestinal risks with piroxicam, ketoprofen, and ketorolac.<sup>2</sup> Of the traditional NSAIDs, low-dose ibuprofen offers the lowest risk. Coxibs are associated with reduced gastrointestinal risk relative to most NSAIDs at equivalent doses. However, coxibs (like NSAIDs) may vary in their effects, and evidence for a reduction in the most clinically important gastrointestinal risks for etoricoxib is weak.<sup>3</sup> Proton pump inhibitors reduce the gastrointestinal risks associated with NSAIDs, and may reduce the risks to a similar level as use of a coxib alone.<sup>4</sup>

# Quiz

This end-of-year quiz will help you test your knowledge of recent drug-safety information. Remember that some articles in *Drug Safety Update* are more relevant for some healthcare professionals than others, so feel free to attempt only the questions related to your specialty!

An answer can be regarded as correct if one part of the whole question is answered correctly.

If you participate in Continuing Professional Development/Continuing Medical Education, you may be able to use the completed quiz as evidence of learning through the reading of past issues of *Drug Safety Update*. We suggest that you keep a copy of the quiz, together with your answers and the bulletin articles. You can claim personal CPD points, for example, with the Royal College of Physicians and the Faculty of Pharmaceutical Medicine.

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

- Q1:** Name the newly identified disorder that can develop in patients with severe renal dysfunction who are given certain gadolinium-containing contrast agents, and give one characteristic of this disorder.
- Q2:** With which class of drugs is intraoperative floppy iris syndrome (IFIS) associated? Name a member of this drug class. During which surgical procedure does IFIS cause complications?
- Q3:** Name a potential class effect associated with dopamine agonists that relates to altered behaviour.
- Q4:** Name an important risk to consider when prescribing hormone-replacement therapy (HRT) for short-term use.
- Q5:** Why is nasal desmopressin no longer indicated for primary nocturnal enuresis?
- Q6:** Name one circumstance when a patient who is prescribed systemic or inhaled steroids should receive a (blue) steroid card.
- Q7:** Why have the indications for systemic piroxicam been restricted? Name a licensed indication, and give the maximum daily dose.
- Q8:** Name a risk factor for osteonecrosis of the jaw with bisphosphonate treatment, and what should be recommended for at-risk patients before starting bisphosphonate treatment?
- Q9:** For which lipid disorder should fibrates be used as first-line therapy?
- Q10:** What types of suspected adverse drug reactions should be reported via the Yellow Card scheme for: a) black-triangle drugs and vaccines (ie, those new to the market and monitored intensively); and b) established drugs and vaccines?

Check your answers on [page 17](#). The answers also include a citation to the original *Drug Safety Update* article, which you can find at [www.mhra.gov.uk/mhra/drugsafetyupdate](http://www.mhra.gov.uk/mhra/drugsafetyupdate)

## Stop press

### Aprotinin: suspension of Marketing Authorisations

See letter to healthcare professionals sent October 2006.

[http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&useSecondary=true&ssDocName=CON2024903&ssTargetNodId=221](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2024903&ssTargetNodId=221)

For further information, please contact the MHRA on 020 7084 2000; for the latest information on aprotinin, see [www.mhra.gov.uk/mhra/safetywarningsandmessagesformedicines](http://www.mhra.gov.uk/mhra/safetywarningsandmessagesformedicines)

In accordance with advice from the Commission on Human Medicines, the Marketing Authorisations (licences) for all aprotinin (Trasylo) products have been suspended. This follows preliminary results of the randomised, blinded, 'BART' study, which found a higher overall death rate associated with use of aprotinin in cardiac surgery than with comparators (tranexamic acid and aminocaproic acid). Recent observational studies have suggested similar risks for aprotinin and increased risks of cardiac, cerebrovascular, and renal adverse effects.

The suspension is expected to last at least 3 months, during which a European-wide review will decide whether licences can be reinstated. In the meantime, aprotinin will still be available, but its use is unlicensed. Prescribers should be aware that responsibility for use of unlicensed products rests with them, and very careful consideration of the risks and benefits for individual patients is needed.

### Lumiracoxib: suspension of Marketing Authorisations

For further information, please contact the MHRA on 020 7084 2000; for the latest information on lumiracoxib, see [www.mhra.gov.uk/mhra/safetywarningsandmessagesformedicines](http://www.mhra.gov.uk/mhra/safetywarningsandmessagesformedicines)

In accordance with advice from the Commission on Human Medicines, the Marketing Authorisations (licences) for lumiracoxib (Prexige▼) have been suspended. This follows a review of the latest worldwide data for spontaneously reported cases of serious hepatotoxicity associated with use of lumiracoxib 100 mg daily (the licensed dose in the EU).

A European-wide review of the risks and benefits of treatment is underway and if necessary further advice will be issued. In the meantime, no further prescriptions for lumiracoxib should be issued.

### Strontium ranelate (Protelos): risk of severe allergic reactions

Access the product information at <http://emc.medicines.org.uk/>

See further information from the European Medicines Agency: [http://www.emea.europa.eu/humandocs/PDFs/EPAR/protelos/PressRelease\\_Protelos\\_41745807en.pdf](http://www.emea.europa.eu/humandocs/PDFs/EPAR/protelos/PressRelease_Protelos_41745807en.pdf)

Strontium ranelate (Protelos▼) is a treatment for postmenopausal osteoporosis. Concerns have arisen about a risk of severe allergic reactions, including drug rash with eosinophilia systemic symptoms (DRESS). These symptoms start with a skin rash, accompanied by a fever, swollen glands, and increased white-cell count; it can also affect the liver, kidneys, and lung. Stopping treatment and corticosteroid therapy usually improves symptoms, but recovery can be slow and there is a risk of symptoms returning during recovery. Healthcare professionals should be alert to the risk of severe allergic reactions. Patients who develop a rash should stop taking the medicine and consult their doctor immediately. Once treatment with strontium ranelate has stopped it should not be re-introduced.

### Talc for pleurodesis: adverse effects

For further information, see [http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&useSecondary=true&ssDocName=CON2032665&ssTargetNodId=364](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2032665&ssTargetNodId=364)

We have recently advised that talc preparations for pleurodesis are to be considered as medicinal products. At present, no such products are licensed. Therefore they may be prescribed only for the special clinical needs of individual patients on the direct personal responsibility of the prescriber. Users should be aware of an increased risk of adverse events, including acute respiratory distress syndrome, with talc preparations of small particle size.

Letters sent by Marketing Authorisation Holders to healthcare professionals are updated monthly on our website at [www.mhra.gov.uk/mhra/HealthcareProfessionalLetters](http://www.mhra.gov.uk/mhra/HealthcareProfessionalLetters)

## Recent letters to healthcare professionals

In November 2007, letters were sent to healthcare professionals to inform them of updated safety information for mycophenolate mofetil (CellCept, congenital malformations after use in pregnancy) and levetiracetam (Keppra, cases of incorrect dose administration).

Physicians also received a letter about inhaled insulin (Exubera▼). The Marketing Authorisation Holder (Pfizer) has decided to stop marketing this medicine because it has not met the needs of doctors who treat patients with diabetes. Pfizer will ensure supplies of Exubera for 3 months while they are changed to other treatment.

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## Other information from the MHRA

See <http://www.mhra.gov.uk/mhra/medicinesregulatorynews>

### New sections on the MHRA website

*Medicines regulatory news* will give the latest information about the regulation of medicines—news about legislation, licensing, standards, product information, advertising of medicines, and much more.

See <http://www.mhra.gov.uk/mhra/devicesregulatorynews>

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Read more about the Commission on Human Medicines, including summaries of minutes from meetings, at <http://www.mhra.gov.uk/mhra/CommissiononHumanMedicines>

To receive an email alert when a new issue of Drug Safety Update is published, send an email to [registration@mhradrugsafety.org.uk](mailto:registration@mhradrugsafety.org.uk)

Complete a Yellow Card online at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)

# Quiz answers

- Q1A:** Nephrogenic systemic fibrosis (NSF, also known as nephrogenic fibrosing dermopathy, NFD). Characteristics: formation of connective tissue in the skin, which becomes thickened, coarse, and hard. These features in turn can lead to contractures and joint immobility. Systemic involvement (eg, lungs, liver, muscles, heart) can occur (Issue 1, August 2007, p2).
- Q2A:**  $\alpha$ -1 adrenoreceptor antagonists (tamsulosin, prazosin, alfuzosin etc); cataract surgery (Issue 1, August 2007, p4).
- Q3A:** Pathological gambling, increased libido/hypersexuality (Issue 1, August 2007, p6).
- Q4A:** Venous thromboembolism, stroke, and coronary artery disease (Issue 2, September 2007, p2).
- Q5A:** Risk of serious hyponatraemia is higher for nasal formulation than for oral formulation
- Q6A:** 1. Those prescribed systemic steroids for more than 3 weeks  
2. Those prescribed a high dose inhaled steroid for prolonged periods (ie, maximum licensed doses when used in conjunction with other steroids such as oral steroids; any off-label high dose; or any dose if used in combination with drugs that inhibit their metabolism—eg, those that inhibit cytochrome P450 such as HIV protease inhibitors)  
3. Any other high-risk patient, at the discretion of the doctor or pharmacist (including patients receiving high-dose nasal steroids) (Issue 2, September 2007, p9; see also *Current Problems in Pharmacovigilance* 2006 [http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&useSecondary=true&ssDocName=CON2023859&ssTargetNodeId=368](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2023859&ssTargetNodeId=368)).
- Q7A:** A higher risk of gastrointestinal toxicity and skin toxicity than other NSAIDs; indications are osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis; maximum daily dose is 20 mg (Issue 3, October 2007, p2).
- Q8A:** Those with cancer, those undergoing chemotherapy, those taking corticosteroids, and those with poor oral hygiene. Dental examination with appropriate preventive dentistry should be considered before bisphosphonate treatment (Issue 3, October 2007, p7).
- Q9A:** Isolated severe hypertriglyceridaemia (Issue 4, November 2007, p2).
- Q10A:** a) Any type of suspected adverse drug reaction; b) Serious suspected adverse drug reactions (Issue 2, September 2007, p10; see also [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk))

## How did you score?

**Score 8–10:** Excellent – *Drug Safety Update* Expert

**Score 5–7:** Very good – great potential

**Score below 5:** Stay up to date: keep reading *Drug Safety Update!*