Drug Safety Update

MHRA

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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Contents

The **Medicines and Healthcare products Regulatory Agency** is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The **Commission on Human Medicines** gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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A number of cases of new-onset heart failure in patients receiving treatment with the antiarrhythmic dronedarone have been reported. Reports of a worsening of symptoms in patients with pre-existing heart failure have also been received.

Furthermore, case reports of liver injury, including two cases of liver failure requiring transplantation, have been reported in patients receiving dronedarone. Some of these cases have occurred early after start of treatment. See article A1 for further information and new monitoring advice.

There have been rare but potentially serious reports of eosinophilic pneumonia associated with the antibacterial daptomycin (Cubicin▼). If eosinophilic pneumonia is suspected, daptomycin should be discontinued immediately and if appropriate the patient treated with corticosteroids. Daptomycin should not be readministered to patients who have experienced eosinophilic pneumonia with this drug—see article A2.

Finally, news this month regarding lenalidomide for multiple myeloma: although multiple myeloma is an independent risk factor for thromboembolic complications, evidence suggests that lenalidomide may further increase the risk of both venous and arterial thromboembolic events (see article A3). Modifiable risk factors for thromboembolic events should be managed wherever possible, and appropriate thrombotic prophylactic medication should be considered. Treatment with lenalidomide must be discontinued and anticoagulation therapy started in patients who experience thromboembolic events. Furthermore this month, article A4 outlines a potential risk of arterial thrombotic events associated with omalizumab for allergic asthma.

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Drug safety advice

A1 Dronedarone: risk of cardiac failure and risk of hepatotoxicity

Use of dronedarone may be associated with:

- an elevated risk of worsening, or new-onset, heart failure
- liver toxicity

Patients should be asked to be vigilant for the symptoms of heart failure or liver toxicity during treatment, and should undergo regular liver function testing

Dronedarone (Multaq▼) is an antiarrhythmic agent indicated in adult, clinically stable patients with history of, or current, non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate. Dronedarone is available as a 400 mg film-coated tablet and the recommended dose is 400 mg twice daily.

Use of dronedarone in patients with heart failure in clinical trials

In a placebo-controlled study of 627 patients with symptomatic congestive heart failure (ANDROMEDA[1]), a higher risk of mortality was observed in the dronedarone group (n=25) compared with the placebo group (n=12; hazard ratio 2.13 [95% CI 1.07–4.25]). Because of this finding, dronedarone is contraindicated in patients who are haemodynamically unstable, including those with symptoms of heart failure at rest or with minimal exertion (ie, New York Heart Association class IV and unstable class III heart failure).

Furthermore, dronedarone is not recommended for clinically stable patients with recent (1–3 months) New York Heart Association class III heart failure or with left ventricular ejection fraction <35% because of limited experience in these patients.

Recently reported cases of new-onset heart failure

Up to Jan 26, 2011, 257 serious cases of new-onset or worsening heart failure (or suspected reactions synonymous with heart failure) have been reported worldwide.

Heart failure may be associated with complications of AF in some patients. In five placebo-controlled studies of dronedarone,[2,3,4,5] the crude incidence of heart-failure events was 369 of 3282 (11.2%) in the dronedarone group and 312 of 2875 (10.9%) in the placebo group.

Risk of adverse liver reactions

Case reports of liver injury, including two cases of liver failure requiring transplantation, have been reported in patients receiving dronedarone. Some of these cases have occurred shortly after start of treatment.

Advice for healthcare professionals:

Cardiac risk

- Patients should be advised to consult a physician if they develop or experience worsening signs or symptoms of heart failure, such as weight gain, dependent oedema, or increased dyspnoea
- If heart failure develops or worsens, consider suspending or discontinuing dronedarone

1 Køber L, et al. N Engl J Med 2008; 358: 2678–68.

2 Touboul, et al. Eur Heart J 2003; 24: 1481–87.

3 Singh BN, et al. N Engl J Med 2007; 357: 987–99.

4 Davy J-M, et al. Am Heart J 2008; 156: 527.e1–527.e9.

5 Hohnloser SH, et al. N Engl J Med 2009; 360: 668–78.

Hepatic risk

- For patients prescribed dronedarone, liver-function tests should be performed:
  - before treatment
  - on a monthly basis for 6 months
  - at months 9 and 12, and periodically thereafter

- Patients currently receiving dronedarone should be contacted within the next month so that liver-function tests can be performed and thereafter they should be tested as described above depending on when treatment was initiated
- If alanine transaminase (ALT) levels are elevated to ≥3× upper limit of normal (ULN), levels should be retested within 48–72 hours. If ALT levels are confirmed to be ≥3× ULN after retesting, dronedarone treatment should be withdrawn
- Patients should be advised to consult a physician if they develop any of the following symptoms of liver injury: abdominal pain or discomfort; loss of appetite; nausea; vomiting; yellowing of the skin or the whites of the eyes; unusual darkening of the urine; itching; or fatigue (especially in association with other symptoms listed above)
- Any patient who is concerned about their treatment should discuss this with a healthcare professional, but patients should not stop taking dronedarone unless they are told to do so
- Please report all suspected adverse reactions to dronedarone via the Yellow Card Scheme at www.yellowcard.gov.uk

Further information

Letter for healthcare professionals
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON105950

BNF section 2.3.2 Drugs for arrhythmias
http://www.medicinescomplete.com/mc/bnf/current/2410.htm

Article citation: Drug Safety Update Feb 2011 vol 4, issue 7: A1.

A2 Daptomycin: risk of eosinophilic pneumonia

There have been rare but potentially serious reports of eosinophilic pneumonia associated with daptomycin (Cubicin▼). If eosinophilic pneumonia is suspected, daptomycin should be discontinued immediately and if appropriate the patient treated with corticosteroids. Daptomycin should not be readministered to patients who have experienced eosinophilic pneumonia with this drug

Daptomycin (Cubicin▼) is indicated for the treatment of complicated skin and soft-tissue infections; right-sided infective endocarditis due to *Staphylococcus aureus*; and *S aureus* bacteraemia when associated with right-sided infective endocarditis or with complicated skin and soft-tissue infections.

Risk of eosinophilic pneumonia

Since daptomycin was licensed in 2006, there have been case reports globally of eosinophilic pneumonia and pulmonary eosinophilia associated with its use. Although the exact incidence of eosinophilic pneumonia associated with daptomycin is unknown, to date the reporting rate is very low (<1/10 000). In severe cases, hypoxic respiratory insufficiency requiring mechanical ventilation may occur, making prompt recognition of the clinical syndrome critical.

Clinical presentation

The most common symptoms of eosinophilic pneumonia include cough, fever, and dyspnoea. Diagnostic findings include increased eosinophils in the lung tissue or bronchoalveolar lavage fluid, along with diffuse infiltrates on chest radiographs. Although clinical suspicion should be raised if there is an elevated peripheral eosinophil count in the setting of pulmonary infiltrates, there have been cases of eosinophilic pneumonia with normal peripheral eosinophil counts.

Further information

See letter for healthcare professionals sent January 2011
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON106073

BNF section 5.1.7 Some other antibacterials
http://www.medicinescomplete.com/mc/bnf/current/129714.htm

Advice for healthcare professionals:

- The most common symptoms of eosinophilic pneumonia include cough, fever, and dyspnoea (see above for further diagnostic criteria). Most cases have occurred after 2 weeks of treatment
- Healthcare professionals should react promptly to signs of eosinophilic pneumonia with daptomycin treatment. Daptomycin should be discontinued immediately and the patient treated with corticosteroids if appropriate
- Daptomycin should not be readministered to patients who have experienced eosinophilic pneumonia with this drug
- Report suspected adverse reactions with daptomycin through the Yellow Card Scheme—see www.yellowcard.gov.uk. When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, and treatment dates

Article citation: Drug Safety Update Feb 2011 vol 4, issue 7: A2.

A3 Lenalidomide: risk of thrombosis and thromboembolism

Patients receiving lenalidomide for the management of multiple myeloma should be closely monitored for evidence of arterial and venous thromboembolic events. Modifiable risk factors for thromboembolic events should be managed wherever possible, and appropriate thrombotic prophylactic medication should be considered. Treatment with lenalidomide must be discontinued and anticoagulation therapy started in patients who experience thromboembolic events

Lenalidomide (Revlimid▼) is authorised in combination with dexamethasone for treatment of multiple myeloma in patients who have received at least one previous treatment. Lenalidomide is an immunomodulatory agent similar to thalidomide, which has antineoplastic, antiangiogenic, and antierythropoietic properties.

Multiple myeloma is an independent risk factor for thromboembolic complications. Evidence from clinical trials and case reports of adverse drug reactions suggests that lenalidomide may further increase the elevated risk of both venous and arterial thromboembolic reactions, including myocardial infarction and cerebrovascular accident, in patients with myeloma.

Clinical trial data

The incidence data in the following table were derived from two multicentre, randomised, double-blind, placebo-controlled, parallel-group studies of lenalidomide plus dexamethasone versus dexamethasone alone in 704 previously treated adults with relapsed or refractory multiple myeloma. The primary efficacy endpoint was time to progression of myeloma for both studies. The median treatment duration in patients assigned lenalidomide and dexamethasone was 44.0 weeks (range 0.1–161.7), and in those assigned dexamethasone alone was 23.1 weeks (0.3–124.0).

	Lenalidomide and dexamethasone	Dexamethasone alone (controls)
Myocardial infarction	1.98%	0.57%
Cerebral vascular events	3.4%	1.7%
Deep venous thrombosis	9.1%	4.3%
Pulmonary embolism	4.0%	0.9%

Case reports of adverse drug reactions

A total of 493 reports of arterial thromboembolic events had been received by the licence holder from all sources worldwide up to Dec 26, 2009. Review of these reports showed a preponderance of cardiac events (mainly myocardial infarctions: 319 reports, 65%). Cerebral vascular events, including transient ischaemic attack, were reported in 17% of cases. The overall reporting rate for arterial thromboembolic events was estimated to be 0.5%, but the true rate is likely to be higher because of under-reporting of reactions.

The licence holder had also received 1079 reports of venous thromboembolic events up to Dec 26, 2009 comprising mainly deep venous thrombosis, with or without pulmonary embolism.

Through the UK Yellow Card Scheme, we have received relatively few reports of thrombosis and thromboembolism in association with use of lenalidomide. Up to Dec 7, 2010, there have been two reports of myocardial infarction and two reports of stroke. Venous thromboembolic events reported in the UK comprise pulmonary embolism (eight cases), deep venous thrombosis (four cases), and unspecified thrombosis (two cases).

Thromboprophylaxis

There was no record of the use of thromboprophylaxis in most patients who were reported to have experienced arterial thromboembolic events (>60%) or venous thromboembolic events (>80%) despite the fact that risk factors, other than myeloma, predisposing to thrombosis were identified in most cases. It is important to note that some of the morbidity and mortality attributable to thromboembolism in patients receiving lenalidomide may be preventable.

Advice for healthcare professionals:

- Patients receiving lenalidomide for the management of multiple myeloma should be closely monitored for evidence of arterial and venous thromboembolic events
- Modifiable risk factors for thromboembolic events should be managed wherever possible (eg, smoking cessation; control of hypertension and hyperlipidaemia)
- Medicines that may increase the risk of thromboembolism, such as oestrogens and erythropoietic agents, should be used with caution during lenalidomide treatment
- Appropriate thrombotic prophylaxis medication should be considered during lenalidomide treatment, particularly in patients with multiple thrombotic risk factors, after careful assessment of the balance of risks and benefits in individual patients
- Treatment with lenalidomide must be discontinued and anticoagulation therapy started in patients who experience thromboembolic events. Once the patient has been stabilised on anticoagulation treatment and any complications of the thromboembolic event have been managed, lenalidomide may be restarted at the original dose, after a reassessment of risks and benefits of treatment. Anticoagulation should then be continued throughout the course of lenalidomide treatment

Further information

European Public Assessment Reports for lenalidomide
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000717/human_med_001034.jsp&mid=WC0b01ac058001d125&murl=menus/medicines/medicines.jsp&jsenabled=true

BNF section 8.2.4 Other immunomodulating drugs
http://www.medicinescomplete.com/mc/bnf/current/200217.htm

Article citation: Drug Safety Update Feb 2011 vol 4, issue 7: A3.

A4 Omalizumab: potential risk of arterial thrombotic events

Use of omalizumab may be associated with an increased risk of arterial thrombotic events. Prescribers should be vigilant for possible thrombotic adverse reactions, and should report these events to us promptly via the Yellow Card Scheme

Omalizumab (Xolair▼) is a monoclonal antibody, which inhibits immunoglobulin E and is licensed for the treatment of severe persistent allergic asthma in patients (age 6 years or older) in whom standard treatment has failed. Omalizumab is usually administered subcutaneously every 2–4 weeks. It is available as a 150 mg powder and solvent for solution for injection.

Arterial thrombotic events with omalizumab

In controlled clinical trials and an unpublished ongoing observational study (EXCELS), a numerical imbalance of arterial thrombotic events (ATEs) was observed in association with use of omalizumab; however, this finding was not statistically significant at the 95% level. ATEs included stroke, transient ischaemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause).

EXCELS is an ongoing observational study of approximately 5000 patients receiving omalizumab and a control group of approximately 2500 patients not receiving this drug. The study aims to evaluate the clinical effectiveness and long-term safety of omalizumab in patients with moderate to severe asthma followed up for 5 years.

The table below summarises interim data from EXCELS and data from controlled clinical trials:

	Arterial thrombotic events per 1000 patient-years of treatment (patient years)		Risk versus controls: hazard ratio, HR (95% CI)
	Omalizumab	Controls	
EXCELS	5.59 (79/14140)	3.71 (31/8366)	Adjusted* HR 1.11 (0.70–1.76)
Controlled clinical trials	6.29 (17/2703)	3.42 (6/1755)	Unadjusted HR 1.86 (0.73–4.72)

*Controlling for baseline cardiovascular risk factors.

Further information

BNF section 3.4.2 Allergen immunotherapy
http://www.medicinescomplete.com/mc/bnf/current/129493.htm?q=xolair&t=search&ss=text&p=1#_129493

Call for reporting

Prescribers should be vigilant for possible thrombotic adverse reactions. All suspected adverse reactions, including arterial thrombotic events, to omalizumab should be reported via the Yellow Card Scheme at www.yellowcard.gov.uk

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Stop press

S1 Dianeal, Extraneal, and Nutrineal peritoneal dialysis solutions: risk of aseptic peritonitis due to possible presence of endotoxin

In December 2010 the potential for raised endotoxin levels was identified in Dianeal, Extraneal, and Nutrineal peritoneal dialysis (PD) solutions manufactured by Baxter. If endotoxin is present there is an increased risk of aseptic peritonitis.

Available evidence suggests that only a small proportion of these PD solutions (manufactured in Castlebar, Ireland) currently marketed are likely to be affected. However, it is not possible to identify affected bags, and all potentially affected products will be recalled and replaced once there is sufficient supply of new unaffected PD solutions for patients. In the meantime replacement Dianeal, Extraneal, and Nutrineal are temporarily being imported from countries outside the EU (from Canada, USA, Singapore, and Turkey) with patient instructions for use.

Advice for healthcare professionals:

- Prioritise new unaffected PD solutions (imported products) over the solutions produced in Ireland, especially for vulnerable patients who critically depend on PD solutions, including those receiving Extraneal with otherwise uncontrollable fluid overload, those with cardiac insufficiency, and those with diabetes that is difficult to control
- Consider other treatment options for other patients (see letter for healthcare professionals)
- Start new patients who require PD on products known to be unaffected (non-Baxter products or imported Baxter products)
- Be alert to symptoms of aseptic peritonitis: cloudy effluent indicating an increased white-cell count, abdominal pain, nausea, vomiting, fever, and negative microbiological culture
- Report any suspected adverse reactions with all PD solutions to Baxter immediately using the adverse-event reporting form (a copy of which is provided with the letter to healthcare professionals), specifying the batch number of product used. Your reports are critically important to the rapid identification of affected batches

Letter for healthcare professionals
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON106073

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