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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Cases of osteonecrosis of the jaw have been reported in patients with cancer treated with bevacizumab or sunitinib, most of whom had received previous or concomitant treatment with intravenous bisphosphonates, which are also known to increase the risk of osteonecrosis of the jaw. See A1 for further information and advice on how to minimise the risk.

Also this month, new clinical data from the USA show that the opioid (dextro)propoxyphene can have serious effects on the electrical activity of the heart, even at normal therapeutic doses. As a result, it is being withdrawn from the US market. In the UK, dextropropoxyphene and paracetamol was licensed as the painkiller co-proxamol until 2007. After UK expert advice that it should be withdrawn from the market over 3 years, we advised that no new patients should start treatment with co-proxamol. In light of these new data, prescribers will wish to reassess the balance of risks and benefits in pre-existing patients who have continued to receive unlicensed treatment with co-proxamol (article H1).

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Drug safety advice

A1 Bevacizumab and sunitinib: risk of osteonecrosis of the jaw

Treatment with bevacizumab or sunitinib may be a risk factor for the development of osteonecrosis of the jaw, particularly if a patient has previously received, or is treated concurrently with, bisphosphonates. Dental examination and appropriate preventive dentistry should be considered before treatment with bevacizumab or sunitinib. Invasive dental procedures should be avoided, if possible, in patients treated with bevacizumab or sunitinib who have previously received, or who are receiving, intravenous bisphosphonates

Further information

See letter sent to healthcare professionals November 2010
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON102775

Information and advice on use of bisphosphonates and risk of ONJ, Drug Safety Update, November 2009
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087832

BNF section 8.1.5 Other antineoplastic drugs
http://www.medicinescomplete.com/mc/bnf/current/4758.htm

Bevacizumab (Avastin) was first authorised in the European Union (EU) in January 2005 for the first-line treatment of patients with metastatic cancer of the colon or rectum. It is also authorised for treatment of patients with metastatic breast cancer; unresectable advanced, metastatic, or recurrent non-small cell lung cancer (other than predominantly squamous-cell histology); and advanced and/or metastatic renal-cell cancer.

Sunitinib (Sutent) was first authorised in the EU in July 2006 and is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour after failure of treatment with imatinib; advanced/metastatic renal-cell carcinoma; and unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults.

Osteonecrosis of the jaw

Cases of osteonecrosis of the jaw (ONJ) have been reported in patients with cancer in association with treatment with bevacizumab or sunitinib, most of whom had received previous or concomitant treatment with intravenous bisphosphonates. Bisphosphonates have very long half-lives and may remain active in bone tissue for many months after discontinuation of therapy.

Bevacizumab is estimated to have been given to more than 800 000 patients with cancer worldwide to date. Data from clinical trials and case reports of adverse drug reactions identified 55 cases of ONJ. Reporting rates appear to be low, with less than one case reported for every 10 000 patients treated.

The number of patients estimated to have received sunitinib worldwide by the end of January 2010 was more than approximately 100 000. At that time, 27 cases of ONJ had been reported in association with sunitinib treatment.

Most cases reported in association with either medicine were confounded by concurrent chemotherapy and concomitant or previous bisphosphonate treatment. Many patients had also received other treatments which are known risk factors for osteonecrosis or ONJ (eg, radiotherapy, glucocorticoids). However, there is sufficient evidence to suspect that bevacizumab and sunitinib may independently increase or contribute to the risk of ONJ.

The mechanism by which bevacizumab or sunitinib may increase the risk of the occurrence of ONJ is not known. Both medicines inhibit angiogenesis, and it would be plausible that this property may play a part in ONJ pathogenesis. Osteonecrosis may result from a temporary or permanent loss of the blood supply to bone. Known risk factors for ONJ are: bisphosphonates; malignant disease; use of corticosteroids; chemotherapy; radiotherapy; poor oral hygiene; smoking; and dental or orofacial surgical procedures.

Continues…

Advice for healthcare professionals:

- Treatment with bevacizumab or sunitinib may be a risk factor for the development of ONJ
- Patients treated who have previously received, or are treated concurrently with, bisphosphonates may be particularly at risk
- Dental examination and appropriate preventive dentistry should be considered before treatment with bevacizumab or sunitinib. Invasive dental procedures should be avoided, if possible, in patients treated with bevacizumab or sunitinib who have previously received, or who are receiving, intravenous bisphosphonates

Article citation: Drug Safety Update Jan 2011 vol 4, issue 6: A1.

A2 Insulin combined with pioglitazone: risk of cardiac failure

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain, and oedema

Further information

BNF section 6.1.1 Insulins
http://www.medicinescomplete.com/mc/bnf/current/4081.htm

National Prescribing Centre information on pioglitazone
http://www.npci.org.uk/blog/?p=2199

Pioglitazone is indicated for the treatment of type 2 diabetes either as monotherapy (brand name Actos▼) or in combination with metformin (brand name Competact▼) and/or a sulphonylurea. Pioglitazone is also indicated in combination with insulin for adults with type 2 diabetes with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

A European review of the increased incidence of cardiac failure when pioglitazone is used in combination with insulin, especially in patients with predisposing factors, has recommended that the product information for insulin should equally reflect this risk and contain appropriate warnings. The product information for pioglitazone already contains warnings about its use in combination with insulin. Warnings are also being added to the product information for all insulin products.

Advice for healthcare professionals:

- Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure
- If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain, and oedema
- Pioglitazone should be discontinued if any deterioration in cardiac status occurs

Article citation: Drug Safety Update Jan 2011 vol 4, issue 6: A2.

A3 **Sitaxentan (Thelin▼): worldwide withdrawal from the market due to hepatotoxicity**

New information regarding the risk of severe, unpredictable hepatic reactions associated with the use of sitaxentan (Thelin▼) means that it will be withdrawn from all markets because the benefit to patients no longer outweighs the risk

See letter sent to healthcare professionals, Dec 2010
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON105736

Sitaxentan (Thelin▼) is an endothelin receptor antagonist, indicated for the treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity.

On Dec 10 2010, the licence holder for sitaxentan announced its decision to withdraw the product from all markets worldwide and to discontinue all ongoing clinical trials. This decision was made after a review of fatal cases associated with hepatic injury, including a reported case from the UK (in 2009) and two cases from clinical trials in India and the Ukraine, which occurred in 2010.

Liver reactions are known side effects of sitaxentan, and warnings have been included in product information since it was first licensed. These warnings were updated to provide further guidance regarding hepatic safety monitoring after the fatal case in the UK.

The new data suggest that serious hepatic toxicity in association with sitaxentan is idiosyncratic and cannot be prevented in all patients. In some patients, development of liver injury was not related to identifiable risk factors, was unlikely to be detected by monthly monitoring, and did not resolve when sitaxentan was discontinued.

Alternative treatments for pulmonary arterial hypertension are available in the UK. Patients should be switched to an alternative treatment as soon as is safely possible. Sitaxentan will continue to be available during the transition period.

Advice for healthcare professionals:

- No new patients should be prescribed sitaxentan
- Patients taking sitaxentan should be switched to an alternative treatment as soon as is safely possible
- Patients should be advised to continue taking sitaxentan and to consult their physician about alternative treatment as soon as possible
- Patients with abnormal liver function test results at the time of sitaxentan discontinuation should be monitored regularly until liver enzymes are within the normal range
- Suspected adverse reactions associated with the use of sitaxentan should be reported on a Yellow Card at www.yellowcard.gov.uk

Advice for patients:

- Patients who are taking sitaxentan or who are participating in clinical trials of the drug should not stop treatment, but should consult their physician to review their treatment as soon as possible
- Patients with any symptoms of liver injury (eg, nausea, vomiting, loss of appetite, fever, unusual tiredness, abdominal pain, or yellow colouring of the skin or eyes [jaundice]) should contact their doctor immediately

Article citation: Drug Safety Update Jan 2011 vol 4, issue 6: A3.

Hot topic

H1 **(Dextro)propoxyphene: new studies confirm cardiac risks**

New clinical data from the USA show that (dextro)propoxyphene can have serious effects on the electrical activity of the heart (resulting in prolongation of the P-R and Q-T intervals, and widened QRS complexes), even at normal therapeutic doses. As a result, products that contain this active, either alone or in combination with acetaminophen (paracetamol), are being withdrawn from the US market, and the Food and Drug Administration (FDA) is advising healthcare professionals to stop prescribing (dextro)propoxyphene to their patients:

See FDA news release, Nov 19 2010
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm234350.htm

and FDA postmarket drug safety information for patients and providers
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm233800.htm

In the UK, dextropropoxyphene and paracetamol was licensed as the painkiller co-proxamol. However, after expert advice in January 2005 that co-proxamol should be withdrawn from the market, all licences had been cancelled by the end of 2007. It is estimated that the withdrawal of co-proxamol from the UK has saved around 300–400 lives each year from self-poisoning, around a fifth of which were accidental.[1]

See Drug Safety Update, Nov 2007, for a reminder issued to prescribers about the withdrawal of co-proxamol
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084675

Furthermore, the FDA's conclusion that the overall balance of risks and benefits is unfavourable is in line with the decision in June 2010 by the European Commission that all products containing dextropropoxyphene should no longer be available across Europe.

Since 2005, most patients have found an acceptable alternative to co-proxamol, after consultation with their healthcare professional. We recognise that there is a small group of patients who have found it very difficult to change from co-proxamol, when alternatives appear to be ineffective or unsuitable. As with any unlicensed medicine there is a provision for the supply of unlicensed co-proxamol, on the responsibility of the prescriber, who can judge the risks and benefits in consultation with the patient. When making this judgment, prescribers will wish to bear in mind the new evidence of cardiotoxicity.

Reminder for healthcare professionals:

- Prescribers will wish to reassess the balance of risks and benefits in each patient of continuing treatment with co-proxamol, taking into account the individual's other medications and any comorbidities, in the light of the new US data
- No new patients should start treatment with coproxamol (see letter to Healthcare Professionals, 31 January 2005: http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con019461.pdf)

Article citation: Drug Safety Update Jan 2011 vol 4, issue 6: H1.

Reference

1 Hawton K, et al. BMJ 2009; 338: b2270
http://www.bmj.com/content/338/bmj.b2270.abstract

Stop press

S1 **Moxifloxacin: use in pelvic inflammatory disease only when other antibacterials are inappropriate or ineffective**

See Drug Safety Update, August 2008
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087781

Further information

BNF section 5.1.12 Quinolones
http://www.medicinescomplete.com/mc/bnf/current/3944.htm

Because of evidence of an increased risk of life-threatening liver reactions and other serious risks (such as QT interval prolongation), oral moxifloxacin (Avelox ▼, a fluoroquinolone antibiotic) should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of the infections below or when these have failed.

This restriction now applies to treatment of mild to moderate pelvic inflammatory disease as well as treatment of acute bacterial sinusitis, acute exacerbations of chronic bronchitis, and community acquired pneumonia (except severe cases).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Article citation: Drug Safety Update Jan 2011 vol 4, issue 6: S1.

S2 **Seasonal flu vaccines: no evidence of increased risk of febrile convulsions in children**

Further information

BNF section 14.4 Vaccines and antisera
http://www.medicinescomplete.com/mc/bnf/current/6454.htm

To date, there is no indication of an excess risk of febrile convulsions in children associated with seasonal influenza vaccines.

From September 2010 to Dec 17, 2010, at least 46 000 children age 6 months to 5 years, have received a seasonal influenza vaccine in the UK. Up to Dec 17, 2010, there were two reports of suspected febrile convulsions associated with seasonal influenza vaccines in children younger than 5 years (data are not available for specific brands). Both children recovered. Analysis of historical data 2000–10 shows that seven cases of febrile convulsions would statistically be expected among the number of children in this age-group who have received a seasonal influenza vaccine. Therefore the number of suspected reports received is within the normal expected range. This will remain under close review.

Further information is available in a report available on our website (see http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON103043)

This analysis follows recent advice that the vaccines Enzira and CSL Biotherapies generic influenza vaccine are not indicated for use in children age less than 5 years this year because of an increased risk of febrile convulsions associated with a similar seasonal influenza vaccine, identified in Australia. Our analysis supports the evidence from Australia that this risk is most likely limited to CSL's vaccine. Children age 6 months to less than 5 years in clinical risk-groups should still receive seasonal influenza vaccination, but health professionals are advised to use the alternative vaccines recommended by the Department of Health (see Drug Safety Update Oct 2010, http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON096813)

Article citation: Drug Safety Update Jan 2011 vol 4, issue 6: S2.

S3 **Implanon contraceptive implant: information for women and healthcare professionals**

BNF section 7.3.2.2 Parenteral progestogen-only contraceptives
http://www.medicinescomplete.com/mc/bnf/current/4580.htm

In light of recent media coverage regarding the contraceptive implant Implanon, we have highlighted our previous advice to support safer use of this product. This follows reports of problems with the insertion and removal of Implanon.

The information is available here:
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON105661

Further information about Implanon and the transition to a new version (called Nexplanon) is available from the October 2010 issue of Drug Safety Update
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON096814

Article citation: Drug Safety Update Jan 2011 vol 4, issue 6: S3.