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 **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 recent review of data has shown that patients treated with thalidomide have an increased risk of arterial thromboembolism, including myocardial infarction and cerebrovascular events, in addition to the established risk of venous thromboembolism. Healthcare professionals should consider venous and arterial thrombotic risk and administer antithrombotic prophylaxis for at least the first 5 months in patients starting thalidomide (see article A1).

Also this month, information about updated dosing for paediatric paracetamol liquids to ensure children receive the optimum dose for their age (article A2).

And finally this month, two reports commissioned by the Department of Health have recently been published on addiction to over-the-counter and prescription-only medicines. See article H1 for further information about the findings of the report, along with a reminder for healthcare professionals to support safer use of these medicines.

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Drug safety advice

A1 Thalidomide: risk of arterial and venous thromboembolism

Patients treated with thalidomide have an increased risk of arterial thromboembolism, including myocardial infarction and cerebrovascular events, in addition to the established risk of venous thromboembolism. Healthcare professionals should consider venous and arterial thrombotic risk and administer antithrombotic prophylaxis for at least the first 5 months in patients commencing thalidomide

Thalidomide (Thalidomide Celgene) is licensed throughout the EU for use in combination with melphalan and prednisone as first-line treatment for patients with untreated multiple myeloma who are age 65 years or older, or those who are ineligible for high-dose chemotherapy. Thalidomide is an immunomodulatory agent, which has antineoplastic, antiangiogenic, and antierythropoietic properties.

See Drug Safety Update, Aug 2008: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085195

Thalidomide Celgene European Public Assessment Report—Product Information: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000823/human_med_001090.jsp&mid=WC0b01ac058001d125&murl=menus/medicines/medicines.jsp

We first published information about Thalidomide Celgene shortly after its UK launch in June 2008 to highlight the key risk of teratogenicity and the risk-minimisation measures in place to prevent exposure of pregnant women to this drug (for further information, see annex II of the Thalidomide Celgene European Public Assessment Report—Product Information).

At that time, we also mentioned other identified serious, or potentially serious, side effects, for which risk-minimisation measures are also in place. These include: venous thromboembolism; neutropenia; thrombocytopenia; peripheral neuropathy (which may be permanent); syncope and bradycardia; serious skin reactions, including Stevens-Johnson syndrome; and somnolence and dizziness.

Postmarketing case reports of thrombosis and thromboembolic reactions

See letter sent to healthcare professionals in May 2011: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON120200

See Drug Safety Update Feb 2011: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON108684

A recent review of global postmarketing data has shown that approximately one third of all thromboembolic reactions reported in association with thalidomide were arterial, most of which were myocardial infarction and cerebrovascular events (54.2% and 19.8%, respectively).

Myeloma is clearly a risk factor for thrombosis; however, the pathophysiology of arterial thrombosis in patients treated with thalidomide is not fully understood. It seems to be an effect associated with this drug class: we have recently reported on a similar risk in association with lenalidomide (Revlimid▼).

Evidence from postmarketing case reports suggests that the risk of arterial thrombotic and thromboembolic reactions is greatest during the first 5 months of therapy. Antithrombotic prophylaxis should therefore be administered for at least the first 5 months of treatment, especially in patients with thrombotic risk factors in addition to multiple myeloma. Antithrombotic prophylactic measures should be prescribed after careful assessment of the individual's underlying risk factors.

A history of thromboembolic events, or concomitant use of erythropoietic agents or other agents such as hormone-replacement therapy, may increase the risk of thromboembolic events. These agents should be used with caution in patients with multiple myeloma who are receiving thalidomide. When using erythropoiesis-stimulating agents, particular attention should be paid to the recommendations in the product information for epoetins regarding haemoglobin concentration because values above 12 g/dL (7.5 mmol/L) are associated with a higher risk of thromboembolic reactions.

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Further information:

BNF section 8.2.4 Other immunomodulating drugs: http://bnf.org/bnf/bnf/current/200217.htm

Advice for healthcare professionals:

- Patients treated with thalidomide have an increased risk of arterial thromboembolism, including myocardial infarction and cerebrovascular events, in addition to the established risk of venous thromboembolism
- Action should be taken to minimise all modifiable risk factors for thromboembolic events (eg, smoking, hypertension, and hyperlipidaemia)
- Healthcare professionals should consider venous and arterial thrombotic risk and administer antithrombotic prophylaxis for at least the first 5 months in patients commencing thalidomide

Article citation: Drug Safety Update July 2011 vol 4, issue 12: A1.

A2 Paracetamol: updated dosing for children to be introduced

Updated dosing for paediatric paracetamol liquids has been developed to ensure children receive the optimum dose for their age

Background

The current recommended doses consist of wide age bands with the option to receive 5 mL or 10 mL within each dose range. As a result, children who are light for their age and receive the maximum recommended dose will receive an amount per kg bodyweight that differs from older, heavier children taking the lower recommended dose within that age band. Consequently, lighter children may currently be receiving a higher dose than needed for an effective therapeutic result, if the parent or carer decides to use the larger dosing option.

To address this, the dosing for liquid paracetamol products for children has been revised to one that is based on narrower age bands with a single dosing option per band. Although dosing for children on a mg/kg bodyweight is standard practice in hospitals, this is not always practical for parents to manage at home. The new posology retains dosing by age bands and the familiar 2.5 mL and 5.0 mL increments.

The changes to paediatric paracetamol dosing have not altered the dose of paracetamol recommended for the treatment of post-vaccination symptoms in children age 2–3 months.

Implementation of updated paediatric paracetamol dosing

The new dosage instructions for paediatric paracetamol will be on products entering the market by the end of 2011. In the meantime, parents and carers should follow the advice currently on the packaging. There is no need to remove any products from shelves. The new packs will also be supplied with a suitable measuring device to assist accurate administration.

The updated dosing will apply equally to prescribed paracetamol for children, and the BNF will be updated accordingly.

Advice for healthcare professionals:

- Parents and carers should be advised to follow the advice on the packaging
- The new dosing will be supplied with a revised patient information leaflet and packaging (entering the market by end 2011)
- All products will be supplied with an administration device to ensure accurate administration

- Doctors may use the new dosing immediately for prescribed paracetamol products

New dosing tables

For paracetamol infant suspension (120 mg/5 mL):

Age: 2–3 months	**Dose**
1. Post-vaccination fever	2.5 mL If necessary, after 4–6 hours, give a second 2.5 mL dose
2. Other causes of pain and fever if your baby weighs over 4 kg and was born after 37 weeks	
• **Do not give to babies less than 2 months of age** • **Do not give more than 2 doses** • **Leave at least 4 hours between doses** • **If further doses are needed, talk to your doctor or pharmacist**	

Child's age	**How much**	**How often (in 24 hours)**
3–6 months	2.5 mL	4 times
6–24 months	5 mL	4 times
2–4 years	7.5 mL	4 times
4–6 years	10 mL	4 times
• **Do not give more than 4 doses in any 24-hour period** • **Leave at least 4 hours between doses** • **Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist**		

For paracetamol six plus suspension (240 mg/5 mL or 250 mg/5 mL):

Child's age	**How much**	**How often (in 24 hours)**
6–8 years	5 mL	4 times
8–10 years	7.5 mL	4 times
10–12 years	10 mL	4 times
• **Do not give more than 4 doses in any 24-hour period** • **Leave at least 4 hours between doses** • **Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist** • **Do not give to children under the age of 6 years**		

Dose for children age 12–16 years: 10–15 mL up to 4 times a day.

Dose for adults and children over 16 years: 10–20 mL up to 4 times a day.

Article citation: Drug Safety Update July 2011 vol 4, issue 12: A2.

A3 Dexrazoxane (Cardioxane): restriction of use to adults with advanced or metastatic breast cancer only

Dexrazoxane is now contraindicated for use in children and adolescents up to age 18 years due to evidence of serious harm in this age-group. Use is restricted to adults with advanced or metastatic breast cancer who have previously received a minimum cumulative dose of 300 mg/m^2 doxorubicin or 540 mg/m^2 epirubicin. The dose ratio for dexrazoxane to be used in combination with doxorubicin has been halved. Dexrazoxane is no longer indicated for use in patients with malignancies other than breast cancer

Dexrazoxane (Cardioxane) is indicated for the prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin in patients with advanced or metastatic cancer after previous anthracycline-containing treatment. An analogue of ethylene diamine-tetraacetic acid (EDTA), it is thought to reduce anthracycline-induced cardiotoxicity by chelation of free iron-containing cations. The drug is also an inhibitor of topoisomerase II and has cytotoxic properties. Most controlled clinical studies of dexrazoxane have been done in patients with advanced breast cancer.

Evidence of harm in children

Two randomised open studies reported a three-fold increase in the incidence of second primary malignancies (particularly acute myeloid leukaemia [AML] and myelodysplastic syndrome) in dexrazoxane-treated children compared with controls.[1,2] A significantly increased risk of other toxicities compared with controls, including severe myelosuppression and severe infection, was also reported in one study.[3]

1 Tebbi CK, et al. J Clin Oncol 2007; 25: 493–500.
2 Salzer WL, et al. Leukemia 2010; 24: 355–70.

3 Schwartz CL, et al. Blood 2009; 114: 2051–59.

Use in adults

Four postmarketing case reports of AML have been reported from France in adults with breast cancer. There is also evidence of increased myelosuppression in patients treated with dexrazoxane. Some studies have observed a higher incidence of death in groups treated with dexrazoxane plus chemotherapy compared with those given chemotherapy alone. The possibility that dexrazoxane was a contributing factor to this imbalance cannot be ruled out.

Furthermore, a significant decrease in tumour response rate has been reported in a study of patients with advanced breast cancer treated with doxorubicin and dexrazoxane compared with those treated with doxorubicin and placebo.[4] Since both dexrazoxane and doxorubicin are topoisomerase inhibitors, it is possible that dexrazoxane may interfere with the antitumour efficacy of doxorubicin.

4 Swain SM, et al. J Clin Oncol 1997; 15: 1318–32.

Further information:

See website of the European Medicines Agency: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Dexrazoxane/human_referral_000277.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580024e99

Advice for healthcare professionals:

- Dexrazoxane is contraindicated for use in children and adolescents up to age 18 years
- Use is restricted to adults with advanced or metastatic breast cancer
- Use of dexrazoxane in combination with adjuvant breast cancer therapy or chemotherapy intended as curative is not recommended
- Patients should be counselled about the risk of leukaemia
- Patients with breast cancer should have received a cumulative dose of at least 300 mg/m^2 doxorubicin or 540 mg/m^2 epirubicin before starting dexrazoxane
- The dose ratio is now 10:1 for dexrazoxane:doxorubicin and for dexrazoxane:epirubicin

Article citation: Drug Safety Update July 2011 vol 4, issue 12: A3.

Hot topic

H1 **Addiction to benzodiazepines and codeine: supporting safer use**

Two reports commissioned by the Department of Health have recently been published on addiction to prescribed and over-the-counter medicines.

See http://www.nta.nhs.uk/uploads/addictiontomedicinesmay2011a.pdf and http://www.kcl.ac.uk/iop/depts/addictions/research/drugs/benzo.pdf, respectively.

- National Treatment Agency for Substance Misuse, May 2011. Addiction to medicine: an investigation into the configuration and commissioning of treatment services to support those who develop problems with prescription-only or over-the-counter medicine
- The National Addiction Centre, King's College London, and School of Social and Community Medicine, University of Bristol, 2011. The changing use of prescribed benzodiazepines and z-drugs and of over-the-counter codeine-containing products in England: a structured review of published English and international evidence and available data to inform consideration of the extent of dependence and harm

Background

See Current Problems in Pharmacovigilance, Jan 1988: http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2024486

Since the 1980s, there have been concerns about the risk of dependence and withdrawal reactions after long term use of benzodiazepines. For more than 20 years, the duration of use of these products has been limited to 2–4 weeks.

Reports of the National Treatment Agency and National Addiction Centre

The data showed that the overall level of prescribing of benzodiazepines decreased between 1991 and 2009. This fall was mainly in the use of benzodiazepines as hypnotics. Use of anxiolytic benzodiazepines increased during this period. The data also showed a gradual increase in sales of over-the-counter codeine-containing medicines since these were placed on the market in 2006.

It was not possible to establish the extent of long-term prescribing of benzodiazepines nationally, but a regional breakdown of data showed very large variations in prescribing practice across England. Benzodiazepine prescribing was highest in the north-west, and prescribing of opiate analgesics was highest in the north-east. The reason for this regional variation is unclear.

Reminder for healthcare professionals:

- Given the risks associated with the use of benzodiazepines, patients should be prescribed the lowest effective dose for the shortest time possible. Maximum duration of treatment should be 4 weeks, including the dose-tapering phase
- Over-the-counter codeine-containing medicines should be used for the short-term (3 days) treatment of acute, moderate pain which is not relieved by paracetamol, ibuprofen, or aspirin alone

OTC codeine advice: see Drug Safety Update Sept 2009: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087912

Management of dependence

Further information:

BNF sections 4.1 hypnotics and anxiolytics (http://bnf.org/bnf/bnf/current/3139.htm) and 4.7.2 opioid analgesics (http://bnf.org/bnf/bnf/current/3491.htm)

The national drug-treatment data suggested that most local areas provide some treatment for people who develop problems with prescription or over-the-counter medicines (without concurrent problems with illegal drugs). Most provision is within primary care and delivered by GPs. Treatment data for those who attend drug-treatment services for problems with prescription or over-the-counter medicines indicate that they engage well and achieve better outcomes than those who use illegal drugs.

Article citation: Drug Safety Update July 2011 vol 4, issue 12: H1.

Stop press

S1 Octagam intravenous immunoglobulin 5% and 10%: lifting of licence suspensions

After an in-depth review of available safety and quality data, the suspension of the licences (marketing authorisations) for Octagam (intravenous human normal immunoglobulin 5% and 10%) has now been lifted. This follows advice from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP).

See Drug Safety Update Oct 2010: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON096802

In September 2010, CHMP recommended suspension of the licences for Octagam after an increased frequency of the known risk of thromboembolic adverse events (eg, stroke, myocardial infarction, and pulmonary embolism).

The increased risk of these events was related to a manufacturing defect, which led to increased levels of thrombogenic substances in the finished Octagam product. A number of measures have now been implemented, including an improved manufacturing process and a thrombogenicity testing before batches of Octagam are released to the market. CHMP was reassured that future production of Octagam would meet the required quality standards and therefore recommended lifting the suspension.

As with all medicines, we will continue to closely monitor the safety of Octagam in the UK.

Further information:

European Medicines Agency Octagam safety review: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2011/04/human_pha_detail_000026.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d126

Reminder for healthcare professionals:

- After implementation of new safeguards and improvements to the manufacturing process for Octagam, the benefits of this product are considered to outweigh the risks
- As with all medicines, any suspected adverse reactions should be reported at www.yellowcard.gov.uk

Article citation: Drug Safety Update July 2011 vol 4, issue 12: S1.

Other information from the MHRA

O1 New learning resource: building and using knowledge on adverse effects of medicines

We have introduced a learning package on pharmacovigilance for clinical practitioners: see: http://www.mhra.gov.uk/ConferencesLearningCentre/LearningCentre/pharmacovigilancelearningmodule/index.htm

This self-directed learning resource covers:

- How information on adverse effects of medicines is assembled
- How to find authoritative information on the risk of individual medicines, and
- How to fill a Yellow Card (www.yellowcard.gov.uk) and contribute to our knowledge on possible harms.

The module concludes with exercises and a reading list for those wanting to learn more. Doctors, nurses, and pharmacists all stand to benefit from the pharmacovigilance module—it will make them more aware of their role in protecting patients from preventable harm.

Article citation: Drug Safety Update July 2011 vol 4, issue 12: O1.