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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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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Following new evidence of cardiovascular, hepatic and pulmonary risk, a review of dronedarone (Multaq) has concluded that the benefits of treatment continue to outweigh the risks for the maintenance of sinus rhythm after successful cardioversion in a limited population of patients with paroxysmal or persistent atrial fibrillation; however, in light of safety concerns dronedarone should only be prescribed after other treatment options have been considered. To support safer use, patients currently taking dronedarone should have their treatment reviewed at the next routine appointment to ensure that they remain eligible for treatment according to the revised prescribing information, including new restrictions on use (see article A1). Regular monitoring of cardiac, liver, and renal function during treatment is also recommended.

Also this month, important news for the availability of medicines for children. Buccolam (buccal midazolam) is a new authorised treatment for prolonged acute convulsive seizures suitable for children age 3 months to 18 years. It is now available on the UK market. Buccolam is an important step forward for the field of paediatrics, as it is the first Paediatric Use Marketing Authorisation to be granted. Further information is available in article A2, including important advice for transfer of patients to this product from previous use of unlicensed medicines.

Finally, recent studies have raised concerns about a possible modest increased risk of some cardiovascular events in postmenopausal women who use calcium and vitamin D supplements to prevent osteoporotic fractures. However, there are limitations to the data and no change to prescribing practice is currently recommended—read our summary of the evidence in article H1.

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Drug safety advice

A1 Dronedarone (Multaq▼): cardiovascular, hepatic and pulmonary adverse events – new restrictions and monitoring requirements

Following new evidence of cardiovascular, hepatic and pulmonary risk, a review of dronedarone has concluded that the benefits of treatment continue to outweigh the risks for the maintenance of sinus rhythm after successful cardioversion in a limited population of patients with paroxysmal or persistent atrial fibrillation; however, in light of safety concerns dronedarone should only be prescribed after other treatment options have been considered.

To support safer use, patients should have their treatment reviewed at the next routine appointment to ensure that they remain eligible for dronedarone treatment according to the revised prescribing information, including new restrictions on use. Regular monitoring of cardiac, liver, and renal function during treatment is recommended

Dronedarone (Multaq▼) is an antiarrhythmic agent available as a 400 mg film-coated tablet with a recommended dose of 400 mg twice daily.

Discontinuation of PALLAS study

The PALLAS study (Permanent Atrial fibriLLAtion outcome Study using dronedarone on top of standard therapy) had been investigating the potential clinical benefit of dronedarone (added to standard therapy) in patients older than 65 years with permanent atrial fibrillation in the reduction of:

- Major cardiovascular (CV) events (ie, stroke, systemic arterial embolism, myocardial infarction, or cardiovascular death); or
- Unplanned cardiovascular hospitalisation or death from any cause

The study was prematurely terminated in July 2011, when an interim analysis showed a significant excess of CV-related deaths, stroke, and hospitalisations due to CV events in the dronedarone group compared with placebo.

Review of risks and benefits

See Drug Safety Update, Feb 2011

A Europe-wide review of the risks and benefits of treatment with dronedarone began in January 2011 because of concerns over reports of liver injury, including two cases of liver failure requiring transplantation. Product information was updated to recommend monthly liver-function testing for the first 6 months of treatment, and at 9 and 12 months after treatment initiation.

The review was extended to include CV and pulmonary safety after the premature termination of PALLAS and several reported cases of pulmonary injury which may be associated with dronedarone.

The review included data from PALLAS and postmarketing data for liver and pulmonary toxicity. The EU Committee for Medicinal Products for Human Use (CHMP) considered that the benefits of treatment now continue to outweigh the risks in a restricted patient population.

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Revised indication

CHMP recommended that dronedarone should now be used only for the maintenance of sinus rhythm after successful cardioversion in patients with paroxysmal or persistent atrial fibrillation (AF). Because of safety concerns, dronedarone should only be prescribed after alternative treatment options have been considered. Dronedarone should not be given to patients with left ventricular systolic dysfunction, or to patients with current or previous episodes of heart failure.

CHMP considered that treatment with dronedarone should be initiated and monitored only under specialist supervision. A number of further contraindications for use and recommendations for monitoring were also endorsed by CHMP.

Further information:

BNF section 2.3.2 Drugs for arrhythmias

Advice for healthcare professionals:

Contraindications:

Dronedarone is now contraindicated in patients with:

- Unstable haemodynamic conditions
- History of, or current, heart failure or left ventricular systolic dysfunction
- Permanent AF (ie, duration ≥6 months or unknown, and attempts to restore sinus rhythm no longer considered by physician)
- Liver and lung toxicity related to previous use of amiodarone

Cardiovascular monitoring:

- Patients should receive regular cardiac examinations, including an ECG at least every 6 months, to identify those who revert to AF. Discontinuation of dronedarone should be considered for these patients
- Discontinue treatment if the patient develops permanent AF
- Patients should be carefully evaluated for symptoms of heart failure during treatment
- Patients should be appropriately anticoagulated as per clinical AF guidelines. International Normalised Ratio (INR) should be closely monitored after initiating dronedarone in patients taking vitamin K antagonists as per the prescribing information for these products

Hepatic monitoring:

- Liver-function tests should be done: before starting treatment with dronedarone; after 1 week of treatment; after 1 month of treatment; then every month for 6 months; at month 9; at month 12; and periodically thereafter

Renal monitoring:

- Plasma creatinine values should be measured before and 7 days after initiation of dronedarone, and renal function should be monitored periodically afterwards. Discontinue treatment in any patients with further elevations of serum creatinine

Pulmonary monitoring

- Cases of interstitial lung disease, including pneumonitis and pulmonary fibrosis, have been reported in association with dronedarone. Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity. If pulmonary toxicity is suspected during treatment, relevant lung examinations should be considered and treatment discontinued if confirmed

Advice for patients:

- Patients should be advised to make a routine appointment to discuss their treatment with the treating physician, but should not stop taking dronedarone unless told to do so

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Reporting of suspected adverse reactions:

- Please report all suspected adverse reactions to dronedarone via the Yellow Card Scheme at www.yellowcard.gov.uk

Article citation: Drug Safety Update Oct 2011 vol 5, issue 3: A1.

A2 Buccal midazolam (Buccolam▼): new authorised medicine for paediatric use—care needed when transferring from unlicensed formulations

Buccal midazolam (Buccolam▼) is a new authorised treatment for prolonged acute convulsive seizures. It is now available on the UK market. Buccal midazolam may be considered as an alternative to rectal diazepam for the treatment of prolonged seizures. Several factors should be considered when transferring patients to the authorised Buccolam product when an unlicensed medicine other than Buccolam has been used previously

Buccolam▼ is a formulation of midazolam suitable for buccal administration in a range of prefilled syringes and doses that are suitable for children aged 3 months to 18 years (2.5 mg in 0.5 mL; 5 mg in 1 mL; 7.5 mg in 1.5 mL; and 10 mg in 2 mL).

Buccolam should only be used by parents or carers where the patient has been diagnosed with epilepsy. For infants aged 3–6 months, treatment should only be in hospital, where monitoring is possible and resuscitation equipment is available.

Transfer to licensed buccal midazolam

Buccal midazolam may be considered as an alternative to rectal diazepam for the treatment of prolonged seizures. Various buccal midazolam preparations have been used in children as unlicensed medicines, including Buccolam prior to authorisation.

Several factors should be considered when transferring patients to the authorised Buccolam product when an unlicensed medicine other than Buccolam has been used previously.

Buccolam is half the strength of some other unlicensed preparations. It contains the hydrochloride salt, whereas some other preparations contain the maleate salt of midazolam. Although there is some suggestion that the maleate salt may be better absorbed in the buccal cavity, there are adequate studies with midazolam hydrochloride to support the dosing schedule authorised for Buccolam. A hospital paediatric unit has recently published its experience of transferring patients to licensed Buccolam

See S Tomlin, *The Pharmaceutical Journal* 2011; 287: 161

Other safety information

- Hypersensitivity to the midazolam, benzodiazepines, or to any of the excipients may occur.
- Midazolam should be used with caution in patients with chronic respiratory insufficiency because it may further depress respiration.
- Midazolam may accumulate in patients with chronic renal failure, or impaired hepatic or cardiac function and should therefore be used with caution in these individuals.

- The most common adverse reactions in clinical trials of buccal midazolam were sedation, somnolence, depressed levels of consciousness, respiratory

depression, and nausea and vomiting.

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Further information from the MHRA:

Drug Safety Update article on the European Paediatric Regulation

Drug Safety Update article on prescribers' responsibilities for off-label or unlicensed use of medicines

MHRA press release for Buccolam

Other information:

Buccolam product information from the European Medicines Agency

NICE guidance for treatment of epilepsy

BNFC section 4.8.1 Control of the epilepsies

Reporting of suspected adverse reactions

Suspected adverse reactions to Buccolam should be reported on a Yellow Card at www.yellowcard.gov.uk

The first Paediatric Use Marketing Authorisation

The 2007 European Paediatric Regulation aims to improve the availability of fully authorised medicines for children in suitable dosage forms. As an incentive for the development of existing out-of-patent medicines specifically for use in children, the Regulation introduced a new type of marketing authorisation (licence) known as a PUMA (Paediatric Use Marketing Authorisation) with the same exclusivity rights as a completely new medicine. A PUMA needs to be supported by studies that comply with a paediatric investigation plan agreed by the European Paediatric Committee. The studies may relate to formulation development, and to safety or efficacy of the product in children.

The European Commission has granted the first ever PUMA to Buccolam.

Article citation: Drug Safety Update Oct 2011 vol 5, issue 3: A2.

Hot topic

H1 Calcium and vitamin D: studies of cardiovascular risk do not support prescribing changes

A recent meta-analysis has raised concerns about a possible modest increase in the risk of some cardiovascular events in postmenopausal women who use calcium and vitamin D supplements to prevent osteoporotic fractures. However, there are limitations to the data and no change to prescribing practice is currently recommended.

A research article[1] in 2010 by Bolland and colleagues seemed to show that calcium supplements without coadministered vitamin D are associated with a modest increased risk of myocardial infarction (MI, hazard ratio [HR] 1.31 [95% CI 1.02–1.67]; p=0.035). Non-significant increases occurred in the incidence of stroke and death; the risk for the composite endpoint (MI, stroke, or sudden death) was of borderline significance (HR 1.18 [1.00–1.39], p=0.057).

1 Bolland MJ, et al. BMJ 2010; 341: c3691

The researchers have recently published[2] a reanalysis of data from a large randomised controlled trial (the Women's Health Initiative study—WHI), and a further meta-analysis of trials of calcium with or without vitamin D versus placebo.

2 Bolland MJ, et al. BMJ 2011; 342: d2040

In the reanalysis of the WHI trial of calcium plus vitamin D versus placebo, the risk of clinical MI was slightly increased in women not self-medicating with calcium supplements at baseline who were randomly assigned to calcium plus vitamin D (HR 1.22 [1.00–1.50]; p=0.054), but this was of borderline significance. There were 209 events of clinical MI in the calcium plus vitamin D group compared with 168 events in the placebo group (an

incidence of 3.5 compared with 2.9 per 1000 patient-years).

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Overall, the reanalyses do not provide conclusive evidence of clinically significant harm, partly because all-cause mortality was not increased in this group (HR 0.99 [0.86–1.14]; p=0.89). Furthermore, for women in WHI who self-medicated with calcium supplements at baseline and who were randomly assigned to calcium plus vitamin D, all-cause mortality was significantly decreased compared with placebo (HR 0.84 [0.73–0.97]; p=0.01).

Inclusion of the WHI subgroup findings (women not self-medicating with calcium supplements at baseline only) in a new meta-analysis of trials of calcium plus vitamin D versus placebo resulted in a slightly lower and more precise risk estimate for MI and stroke associated with calcium plus vitamin D (relative risk 1.16 [95% CI 1.02–1.32], p=0.02). However, there was no increase in the risk of all-cause death.

The reanalysis was reviewed by the Commission on Human Medicines (CHM) and its expert advisors. There were concerns over methodology and data interpretation, and they advised that the data did not provide convincing evidence that calcium and vitamin D supplements were associated with an increased risk of cardiovascular events. They considered that any further research should be carefully evaluated and that it would be desirable to study separately the effects of calcium and vitamin D on cardiovascular risk.

Concerns over methodology and data interpretation included that, for the reanalysis, the increased risk of MI (or the composite of MI or stroke) in women not taking calcium supplements at baseline was only just significant and there was no increased risk in overall mortality in that group. Furthermore, for the new meta-analysis, concerns included: inclusion of trials with different endpoints; exclusion of more than half the participants in the WHI trial; a small, marginally significant increased risk of MI and stroke in the subgroup but not in the overall WHI trial; and multiple testing, which increases the risk of false-positive results.

Finally, there may be alternative explanations for the findings, such as misclassification bias whereby upper gastrointestinal side effects (which are common with calcium supplements) are misclassified as symptoms of cardiac disease.

Advice for healthcare professionals:

- Prescribers should consider the potential benefits and risks of using calcium and vitamin D for prevention of osteoporotic fractures on an individual basis in line with NICE guidance. Prescribers should consider offering these supplements to postmenopausal women who receive treatment for osteoporosis (eg, with bisphosphonates), unless they are confident that the patient has an adequate calcium intake and is vitamin D replete
- The National Osteoporosis Society advises that increasing dietary intake in those with low intakes of calcium and vitamin D is considered preferable to supplements. They also advise that supplementation may be warranted, but needs to be done with consideration based on dietary intake

See:
NICE guidance on drugs for the primary prevention of osteoporosis;

NICE guidance on drugs for the secondary prevention of osteoporosis

Further information:

BNF section 6.6 Drugs affecting bone metabolism—osteoporosis

Article citation: Drug Safety Update Oct 2011 vol 5, issue 3: H1.

Stop press

S1 **Enzira/CSL Biotherapies and Viroflu/Inflexal V influenza vaccines and risk of febrile reactions in children under 5 years: use alternative vaccines in under 5s and report suspected adverse reactions**

Prescribers are reminded that Enzira and CSL Biotherapies generic influenza vaccines (both manufactured by CSL and marketed by Pfizer) should not be given to children younger than 5 years. These vaccines are not authorised for use in this age-group after the increased risk of febrile convulsions observed in Australia last year.

See Drug Safety Update, Oct 2010

CSL also supplies starting materials for the manufacture of another flu vaccine, Viroflu and Inflexal V (both manufactured by Crucell UK), which will be supplied in the UK this year. It is not known if Viroflu/Inflexal V may also carry a risk of febrile convulsions. However, because of a higher than expected frequency of fever above 39^{0}C seen in a clinical trial in children, the licence for Viroflu/Inflexal V has been amended to advise caution when using in children younger than 5 years. Because a risk of febrile convulsions cannot be excluded, Viroflu/Inflexal V should only be used if a suitable alternative flu vaccine is not available. This advice is endorsed by the Department of Health.

See advice from Department of Health

It is important that children older than 6 months who are in clinical risk groups receive flu vaccination, and the alternative vaccines should be used as recommended.

For further information, see letter from the Department of Health on the influenza immunisation programme 2010/11

We proactively monitored the safety of the CSL vaccines and other seasonal flu vaccines during the 2010–11 flu season, with help from Yellow Card reporters. We found no evidence of an increased risk of febrile convulsions in children associated with other seasonal influenza vaccines, suggesting that this risk is limited to the Enzira and CSL Biotherapies generic influenza vaccines. ViroflulnflexalV was not used in the UK during 2010–11.

See Drug Safety Update, Jan 2011

In the forthcoming seasonal immunisation campaign we will continue to closely monitor the safety of all flu vaccines. In particular, we ask you to help by promptly reporting any cases of febrile convulsion occurring within 72 hours of receiving a flu vaccine. It is very important that the brand name of the vaccine given, and batch number if available, are reported to us. If you do not have this information at hand, please still report to us and we will follow-up with you for further information.

Further information:

BNF section 14.4 Vaccines and antisera

Reports of febrile convulsions or any suspected adverse reaction can be sent online to www.yellowcard.gov.uk

Article citation: Drug Safety Update Oct 2011 vol 5, issue 3: S1.

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S2 **Aqueous calamine cream: do not use before X-ray examination**

Further information:

BNF section 13.3 Topical local anaesthetics and antipruritics

Aqueous calamine cream is used for the relief of symptoms of mild sunburn and other minor skin conditions. It contains zinc oxide 3.0% w/w. If used on the skin before an X-ray examination, the zinc oxide in this product may mimic intramammary calcifications, which can be an important indicator of early breast cancer.

After a review of the available safety information, information has been added to the product label and leaflet advising not to apply aqueous calamine cream onto the skin before an X-ray examination because it may affect the outcome of the radiograph.

Article citation: Drug Safety Update Oct 2011 vol 5, issue 3: S2.