Drug Safety Update

MHRA

Latest advice for all medicines users

The monthly newsletter from the **Medicines and Healthcare products Regulatory Agency** and the **Commission on Human Medicines**

Volume 2, Issue 7 **February 2009**

Contents

Our pharmacovigilance work involves continually looking at new data on the safety of medicines. Our drug safety advice this month highlights that new data, rather than necessarily changing advice, can often confirm previous advice we have given to support best practice. Tibolone is a synthetic hormone therapy for first-line treatment of menopausal symptoms and for second-line prevention of osteoporosis in women at high risk. Recent data show that tibolone significantly increased the risk of breast cancer recurrence in women with a history of breast cancer compared with placebo. Consistent with conventional hormone-replacement therapy, tibolone is contraindicated in women with known or suspected breast cancer, and in those with a history of breast cancer (p 2). However anecdotal evidence suggests that tibolone is sometimes used off-label for treatment of vasomotor symptoms in women with a history of breast cancer.

Also this month, we discuss two recently published epidemiological studies on the thrombotic cardiovascular risk associated with use of non-steroidal anti-inflammatory drugs (NSAIDs) in the general population. Findings of these studies support current advice that patients should use the lowest effective dose and for the shortest duration necessary to control symptoms (p 3).

Finally you might be interested in our Yellow Card reporting guidance on p 4. This comprehensive guide can easily be saved or printed to serve as a reminder to you and your colleagues about the importance of telling us about any suspected adverse drug reactions—remember, you do not have to prove any link.

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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 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

Tibolone (Livial): increased risk of breast cancer recurrence

Keywords: tibolone, Livial, breast cancer, vasomotor symptoms, hormone-replacement therapy, HRT

Tibolone increases the risk of breast cancer recurrence in women with a history of breast cancer. Tibolone should not be used in women with known or suspected breast cancer, or in those with a history of breast cancer

Tibolone (Livial) is a synthetic hormone therapy that is licensed as a first-line treatment for menopausal symptoms and a second-line therapy for prevention of osteoporosis in postmenopausal women who are at high risk of future fracture.

Tibolone and breast cancer

There are limited clinical trial data and conflicting epidemiological evidence regarding the risk of breast cancer in tibolone users. The Million Women Study[1] found that women who used tibolone had a significantly higher risk of breast cancer than did never-users (relative risk 1·5 [95% CI 1·3–1·7]). The level of increase was comparable with that in women who used oestrogen-only hormone-replacement therapy (HRT), and was significantly lower than the level in combined HRT users. Risk increased with longer duration of use, and returned to baseline within a few years of stopping treatment. A study using the General Practice Research Database found no significant risk of breast cancer with tibolone use.[2] Unlike conventional HRT, tibolone has a limited effect on mammographic density.

1 Million Women's Steering Committee. *Lancet* 2003; **362:** 419–27.

2 Opatrny L, et al. *BJOG* 2008; **115:** 169–75.

For more information about the General Practice Research Database, see http://www.gprd.com

Treatment for breast cancer (eg, tamoxifen) can commonly exacerbate menopausal symptoms. Although tibolone is contraindicated in women with known or suspected breast cancer, and in those with a history of breast cancer, anecdotal evidence suggests that tibolone is sometimes used off-label for treatment of vasomotor symptoms in women with a history of breast cancer; tibolone may be perceived as being safer than conventional HRT in this respect.[3]

Recently, the LIBERATE randomised controlled trial in women with previous breast cancer was stopped 7 months early because it was unable to establish non-inferiority of tibolone compared with placebo for risk of breast cancer: importantly, it identified a significantly increased risk of breast cancer recurrence.

3 Trinh X-B, et al. *Eur J Obstet Gynecol Reprod Biol* 2006; **124:** 207–11.

LIBERATE trial

The LIBERATE trial was designed to investigate whether tibolone is effective and safe to use in women with a history of breast cancer.[4]

This multicentre, randomised, double-blind, placebo-controlled trial recruited women who had had surgery for primary breast cancer within the last 5 years (n=1579 in tibolone group and 1569 in placebo group). Its primary aim was to show that tibolone was non-inferior to placebo with respect to breast cancer recurrence.
The study was stopped early because it identified a significantly increased frequency of breast cancer recurrence in the tibolone group compared with the placebo group (237 *vs* 165 cases, respectively, hazard ratio 1·4 [95% CI 1·1–1·7]). The trial also confirmed a higher incidence of vaginal bleeding or spotting and increased endometrial thickness in the tibolone group compared with placebo.

4 Kenemans P, et al. *Breast* 2007; **16** (suppl 2): S182–89.

For an overview of HRT, see the HRT floor on www.npci.org.uk, for eg: http://www.npci.org.uk/therapeutics/therap/hrt/workshops/workshop_60minute_elearn_event1.php
For an overview on breast cancer see the NPCi breast-cancer floor, for eg: http://www.npci.org.uk/therapeutics/therap/breast/workshops/workshop_60minute_elearn_event1.php

Advice for healthcare professionals:

Tibolone (or conventional HRT) should not be used in women with known or suspected breast cancer, or in those with a history of breast cancer

Non-steroidal anti-inflammatory drugs: cardiovascular risk

Keywords: non-steroidal anti-inflammatory drug, NSAIDs, cardiovascular, myocardial infarction, MI

Results of two recently published epidemiological studies lend support to the view that some increase in thrombotic cardiovascular risk may apply to all NSAIDs users, irrespective of their baseline risk, and not only to chronic users. The absolute increase in risk for 'healthy' users is very low. Current advice remains that patients should use the lowest effective dose and the shortest duration of treatment necessary to control symptoms. Overall evidence continues to indicate that naproxen is associated with a lower thrombotic risk than coxibs. For ibuprofen, no significant increase in risk has been identified for doses of up to 1200 mg daily

Two recently published epidemiological studies (one using the UK THIN [The Health Improvement Network] database[1] and one using Danish national registries[2]) investigated the risk of cardiovascular events in association with non-steroidal anti-inflammatory drugs (NSAIDs) for the general population. The results of these studies lend support to the view that an increase in thrombotic risk applies to all NSAIDs users, irrespective of their baseline risk, and not only to chronic users.

1 García Rodríguez LA, et al. *J Am Coll Cardiol* 2008; **52:** 1628–36.

2 Fosbøl EL, et al. *Clin Pharmacol Ther* 2009; **85:** 190–97.

New evidence supports current advice to use lowest dose for shortest duration

See Drug Safety Update December 2007, p 13; www.mhra.gov.uk/mhra/drugsafetyupdate; see also online http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2025040

Cardiovascular and gastrointestinal toxicity are the two most important safety concerns for NSAIDs. After a comprehensive Europe-wide review of clinical-trial and epidemiological data in October 2006, the Commission on Human Medicines gave advice on the latest evidence for cardiovascular thrombotic risk—ie, that NSAIDs may be associated with a small increased risk of thrombotic events such as myocardial infarction or stroke especially when used at high doses and for long-term treatment.

The findings from the two recent studies are consistent with, and show external validity for, the 2006 review of NSAIDs. Current advice therefore remains that patients should use the lowest effective dose and the shortest duration of treatment necessary to control symptoms.

UK THIN study

Has your colleague seen this bulletin?

This retrospective population-based cohort study[1] with nested case-control analysis aimed to assess the association between NSAID use (including coxibs) and risk of non-fatal MI in the general population. The final cohort consisted of 716 395 patients followed up for about 4 years. The number of non-fatal incident MIs was 8852. Relative risk of MI in current users (ie, those who used NSAIDs in the week immediately preceding the event) was 1·34 (95% CI 1·23–1·47). This level of risk (1·4 additional MIs per 1000 users per year) falls well within the additional 3 thrombotic cardiovascular events per 1000 users per year (compared with no treatment) that was previously estimated for coxibs.

A limitation of the THIN database is that over-the-counter sales of ibuprofen are not captured; another is that many subgroup analyses are too small to give reliable risk estimates. The inherent problem with a database study like this is that it is prone to biases and confounding factors (ie, those that are associated with NSAID use and are independently associated with cardiovascular risk). Although attempts were made to correct for these factors, it is possible that some effects may not have been identified or accounted for in the analyses. Nevertheless, the results of this study are consistent with conclusions of the wide-ranging 2006 review.

Danish registry study

This cohort study[2] aimed to assess whether the increased risk of cardiovascular events observed in clinical studies applies to healthy people (defined as having no previous hospital admissions in the previous 5–10 years and no prescriptions for specific concomitant medications). This study looked at non-selective NSAIDs and at coxibs. The investigators concluded that use of any NSAIDs studied (but particularly rofecoxib, celecoxib, or diclofenac), especially at high doses, increases the risk of serious cardiovascular events in healthy individuals, even in the short-term. However, the absolute increase in risk for 'healthy' users is very low.

Despite some limitations of this study, including questions over the study design, pattern of NSAID use, and the definition of 'healthy' the results of this study are also in line with the conclusions of the 2006 review.

Conclusions of new studies

The new studies have found an increased cardiovascular risk with all users of NSAIDs, not only those with baseline cardiovascular risk factors. This risk was noted after relatively short-term use (and may increase with increasing duration of use). It occurred in association with low doses of some NSAIDs (and increased with dose for some NSAIDs), and occurred in association with celecoxib, high-dose diclofenac, and high-dose ibuprofen (>1200 mg/day). No detectable effect on cardiovascular risk was shown for naproxen.

Information and advice for healthcare professionals:

- Two recent epidemiological studies lend support to the view that some increased cardiovascular risk may apply to all NSAIDs users, irrespective of their baseline risk, and not only to chronic users. However, the greatest concern relates to chronic use of high doses (especially for coxibs and diclofenac)
- Patients should use the lowest effective dose and the shortest duration of treatment necessary to control symptoms. The need for long-term treatment should be reviewed periodically
- Overall evidence continues to indicate that naproxen is associated with a lower thrombotic risk than coxibs. For ibuprofen, no significant risk has been identified for doses of up to 1200 mg daily
- The findings from these studies do not change previous advice to support safer NSAID use that was issued in 2006 from the Commission on Human Medicines after a Europe-wide review

see http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2025040

Yellow Card Scheme update

Reporting suspected adverse drug reactions with the Yellow Card Scheme

The MHRA and the Commission on Human Medicines (CHM) run the UK's spontaneous adverse drug reaction (ADR) reporting scheme - called the Yellow Card Scheme. This receives reports of suspected ADRs from healthcare professionals and patients.

What is an ADR?

An adverse drug reaction is an unwanted or harmful reaction experienced following the administration of a drug or combination of drugs under normal conditions of use and is suspected to be related to the medicine.

How common are ADRs?

ADRs are common. A study of hospital admissions in the UK [1] found that:

- 6.5% of admissions were related to ADRs
- Projected annual cost to the NHS is £466 million
- Over 2% patients admitted with an ADR died, suggesting an overall fatality rate from ADRs within the population of 0.15%
- 72% of ADRs were definitely or possibly avoidable

How does the Scheme work?

The Yellow Card scheme relies on healthcare professionals to voluntarily report ADRs. It acts as an early warning system for the identification of previously unrecognised reactions and enables us to identify risk factors, outcome of the ADR and other factors that may affect clinical management.

The value of the scheme has been demonstrated many times and it has helped to identify many safety issues. For example Yellow Cards about liver toxicity with black cohosh resulted in improved safety warnings. The continued success of the scheme depends on the vigilance of UK healthcare professionals and your willingness to report suspect ADRs. Every report can make a difference.

What do I report?

- Report **all** suspected ADRs to new drugs (i.e. drugs marked with an inverted black triangle (▼). The Intensive monitoring list gives details of all black triangle drugs and is updated monthly
- Report serious suspected reactions to established medicines including over-the-counter (OTC) and herbal medicines

Serious reactions are those which are:

- Fatal
- Life-threatening
- Disabling
- Incapacitating
- Result in, or prolong, hospitalisation
- Medically significant
- Congenital abnormalities

Examples of serious reactions are available on our website

Areas of special interest (e.g. retinopathy)

We are keen to receive Yellow Cards on:

- All suspected ADRs in children
- All suspected ADRs in the elderly
- Delayed drug effects (e.g. retinopathy)
- Congenital abnormalities
- Suspected ADRs to HIV medicines

Causality does not need to be established. You only need to have a suspicion that a reaction is related to a drug.

How do I report?

The easiest way to report is using the electronic Yellow Card at www.yellowcard.gov.uk. It is quick and simple, and you do not have to worry about finding a post-box. You can register on the site and the Yellow Card can be saved at any time. You can keep track of the Yellow Cards you send. The website gives full instructions on how to complete the Yellow Card.

Yellow Cards are also available:

- By downloading a Yellow Card to print out
- By writing to: MHRA, CHM Freepost, London SW8 5BR
- By emailing pharmacovigilance@mhra.gsi.gov.uk
- From the British National Formulary (BNF)
- From the ABPI Medicines Compendium
- From the MIMS Companion

What information should I include?

Please include four critical pieces of information on the report:

1. Patient details

Basic information about the patient is vital in assessing reports and obtaining further information. Please provide at least one of the following:

- Patient sex, age at the time of the reaction and weight if known
- Patient's initials and local identifier which can identify the patient to you

All information is held in confidence.

2. Suspect drug(s)

Name of the drug(s) suspected to have caused the reaction. Include daily dose, dose frequency/schedule, start and stop dates and route of administration. If it is a vaccine, please quote brand and batch number.

3. Suspect reaction(s)

Describe the suspected reaction(s), including a diagnosis if relevant. Include the date when the reaction occurred,

1 Pirmohamed M, et al. *BMJ*; 2004; **329:** 15–19.

seriousness, any treatment given and outcome.

If the reaction has already been reported (e.g. by another healthcare professional or the patient) but you have additional information to report, please submit a Yellow Card as we can detect duplicate reports and link the information.

4. Reporter details

Please include your name and full address. This is so we can acknowledge receipt of the report, and follow up your report for further information if necessary.

Additional information

We would be grateful for any additional information that you think might be relevant to the reaction:

- Other drugs taken in the last three months prior to the reaction, including OTC and herbal medicines
- Any information on rechallenge with the suspect drug(s)
- Relevant medical history, including allergies
- Relevant test results
- For congenital abnormalities, please state all other drugs taken during pregnancy and the date of the last menstrual period

If the patient was not taking any other drugs, or if no other information is available, please indicate this.

All the information you provide helps us to interpret the case and evaluate safety issues. Please provide as much relevant information as is readily available because this will reduce the need for follow-up, but do not delay reporting just because some details are not known.

Reporting by patients

Patients are welcome to directly report suspected ADRs to us through the Yellow Card Scheme.

As healthcare professionals, you are well placed to inform patients of the Yellow Card Scheme. We therefore ask you to encourage patients to report all possible side effects that were bad enough to interfere with everyday activities, and all possible reactions not listed in the patient information leaflet included with their medicine.

Patients can report online at www.yellowcard.gov.uk or on a Yellow Card form which can be found at pharmacies. Alternatively they can call the Yellow Card hotline on **0808 100 3352**.

Further information on patient reporting is on the MHRA website.

Should healthcare professionals continue to report with patients now reporting?

Yes. Healthcare professionals continue to provide the vast majority of Yellow Card reports, and have a professional responsibility to report suspected ADRs to the MHRA. We ask that you continue to report to the scheme as your reports are vital in gaining clinical information and perspective on possible side effects. We believe that this information can be complemented by patient reporting.

How is Yellow Card data used to improve patient safety?

Information gathered from Yellow Card reports made by patients and healthcare professionals is continually assessed by a team of safety experts made up of doctors, pharmacists and scientists who study the benefits and risks of medicines.

If a new side effect is identified, information is carefully considered in the context of the overall side effect profile for the medicine, and how the side effect profile compares with other medicines used to treat the same condition. We take action, whenever necessary, to ensure that medicines are used in a way that minimises risk while maximising patient benefit.

In assessing the safety of medicines, the MHRA receives advice from the CHM, which is the Government's independent scientific advisory body on medicines safety. The CHM is made up of experts from a range of clinical and scientific specialities and includes lay representatives.

From the data collected on Yellow Card reports the following can result:

1. Changes to the medicine's Summary of Product Characteristics (e.g. maximum doses, addition of contraindications or cautions in patient populations or concomitant disease)
2. Publication of safety information in Drug Safety Update. You can subscribe to have an e-mail notification sent to you when it is published each month (email registration@mhradrugsafety.org.uk)
3. 'Dear Healthcare professional' letters from the chairman of the CHM
4. Listings of suspected ADRs to drugs, Drug Analysis Prints (DAPs, www.mhra.gov.uk/DAPS)
5. Rarely, withdrawal of a medicine if there is a risk to public health

Reporting by healthcare professionals is key

Every healthcare professional has an important role to play in the Yellow Card Scheme, both by raising awareness of patient reporting, and by continuing to identify and report ADRs through the scheme.

A better understanding of adverse drug reactions allows us to give advice on how medicines can be used more safely. If you suspect that a reaction experienced by your patient is associated with a medicine being taken, then you should report. Please do not be put off from reporting just because you are uncertain about cause and effect.

DON'T DELAY REPORT TODAY!

Stop press

Toremifene (Fareston): risk of QT prolongation

To view updated product information, press release, and question and answer document, see the European Medicines Agency website at http://www.emea.europa.eu

Toremifene (Fareston) is an oestrogen receptor antagonist. Currently it is not widely used in the UK, but remains a licensed option to treat hormone-dependent metastatic breast cancer in postmenopausal women.

A European assessment has concluded that toremifene is associated with a dose-dependent increase in QT interval, which carries a risk of serious cardiac arrhythmia. The Summary of Product Characteristics has been updated to include new contraindications and warnings.

Methylphenidate: new guidance for use in treatment of ADHD

The European Medicines Agency has completed a review of the safety of **methylphenidate** in the treatment of attention-deficit/hyperactivity disorder (ADHD). The Agency's Committee for Medicinal Products for Human Use has concluded that the benefits of medicines that contain methylphenidate continue to outweigh any risks when used in their licensed indication to treat children age 6 years or older and adolescents for ADHD. However, the Committee concluded that prescribing information should be made consistent and should be updated with further guidance on pretreatment screening and continued monitoring of patients.

For further information from the European Medicines Agency, see http://www.emea.europa.eu

Look out for next month's Drug Safety Update (March 2009 issue) for full information and advice from this review.

Latest safety information online

Safety information homepage:
http://www.mhra.gov.uk/Safetyinformation/index.htm
Drug alerts:
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Drugalerts/index.htm
Safety warnings for medicines:
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/index.htm
Product-specific information:
http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/index.htm

Stay up to date with the latest safety information for medicines using the MHRA website. Our safety information section lists the latest letters sent to healthcare professionals that inform of updated safety information for a medicine, and also lists drug alerts—recall notices for defective medicines. We also have a section of information and advice for specific medicines (eg, antiepileptics, herbal remedies, and smoking-cessation aids) which give a general safety overview.

Correction: Temsirolimus—severe hypersensitivity reactions during infusion

An article about the risk of severe hypersensitivity reactions during infusion of temsirolimus in the January issue of Drug Safety Update (p 3) contained an error in the final bullet point of advice for healthcare professionals.

The first sentence in the final bullet point of advice should have read: "If infusion is to be resumed, diphenhydramine (or similar antihistamine) and an H_2-receptor antagonist (20 mg famotidine intravenously or 50 mg ranitidine intravenously) should be administered approximately 30 min before restarting temsirolimus infusion".

Other information from the MHRA

Patient Information Leaflet of the month: Actonel Once-a-Week

See PIL of the month at: http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleaflets andpackaging/Patientinformationleaflet(PIL) ofthemonth/index.htm

Patient information leaflets (PILs) are improving in quality as a result of new legal obligations on manufacturers to test the documents with potential patients. Testing makes sure that the presentation of the information enables patients to find and understand key messages for safe use about the medicine within the PIL and thereby enables them to use the medicine safely and effectively. To promote this new initiative, we are publishing a series of examples of best practice on our website. The latest in the series is for **Actonel Once-a-Week**. This product contains **risedronate sodium**, a bisphosphonate, and is used in the treatment of osteoporosis.

Consultation: measures to strengthen the medicines' supply chain

Further information is available at http://www.mhra.gov.uk/NewsCentre/CON033662

We would like to seek your views on proposals to strengthen the medicines' supply chain in the UK in light of increasing threat from counterfeit medicines. This consultation also seeks views on proposed changes to EU legislation to combat counterfeiting. We want to hear how the proposals may affect you, what benefits they may bring, and what costs they may incur.

The consultation closes on March 13, 2009.

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

Sign up to receive an email alert when a new issue is published: email registration@mhradrugsafety.org.uk

Report a suspected adverse drug reaction at http://www.yellowcard.gov.uk

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