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Our ref: PLW/3/8

24 October 2006

IMMEDIATE MESSAGE TO:

1. Directors of Public Health
2. Medical Directors in NHS Boards
3. Specialists in Pharmaceutical Public Health
4. NHS 24

SAFETY OF SELECTIVE AND NON-SELECTIVE NSAIDs

Please see for immediate transmission (see list below) a copy of a message from Professor Gordon Duff, Chairman, Commission on Human Medicines about new data assessed by the Commission and outcome of the European review on the small increased risk of thrombotic events (heart attack and stroke) associated with non-selective NSAIDs when used at high doses and for long–term treatment.

Please could Medical Directors in NHS Boards forward on to:-

- All General Practitioners – please ensure this message is seen by all practice nurses and non-principals working in your practice and retain a copy in your 'locum information pack'.
- Deputising Services
- Directors of Nursing
- Chief Pharmacists to forward on to Medicines Information Pharmacists
- Medical Prescribing Advisers
- All Hospital Doctors

Please could Directors of Public Health forward the message to:

- Chief Executives, NHS Boards

Please could Specialists in Pharmaceutical Public Health forward the message to:-

- Community Pharmacists

Thank you for your co-operation.

Yours sincerely

Pamela S Warrington.

PAMELA S WARRINGTON
Deputy Chief Pharmaceutical Officer

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Dear Colleague,

Safety of Selective and non-selective NSAIDs

I wrote to you last about the safety of non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX2 inhibitors (coxibs) in August 2005, and since that time further evidence has emerged. New data have been assessed by the Commission on Human Medicines (CHM) and a European review has now been completed.

New information on non-selective NSAIDs

Non-selective NSAIDs may be associated with a small increased risk of thrombotic events (such as heart attack or stroke) when used at high doses and for long-term treatment.1

Evidence for diclofenac (particularly at the 150 mg dose) suggests that this drug may have a small thrombotic risk, similar to that of licensed doses of etoricoxib, and possibly other coxibs. These new data are from the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) study,2 which is due to be published soon.

For ibuprofen, at high doses (e.g. 2400 mg a day) there may be a small thrombotic risk, but overall, at low doses (e.g. 1200 mg or below), epidemiological data do not suggest an increased risk of myocardial infarction.

Naproxen is associated with a lower thrombotic risk than coxibs and, overall, epidemiological data do not suggest an increased risk of myocardial infarction; however, some increase in risk cannot be excluded on the basis of available evidence.1

For all NSAIDs thrombotic risk is likely to be greater when used at high doses and for long-term treatment.1

General advice on prescribing NSAIDs and coxibs

The lowest effective dose of NSAID or coxib should be prescribed for the shortest time necessary for control of symptoms. The need for long-term treatment should be reviewed periodically.

Prescribing should be based on the safety profiles of individual NSAIDs or coxibs and on individual patient risk profiles (eg, gastrointestinal and cardiovascular).

Prescribers should not switch between NSAIDs without careful consideration of the overall safety profile of the products, a patient's individual risk factors, and patient preference.

Concomitant aspirin (and possibly other antiplatelet drugs) greatly increase the gastrointestinal risks of NSAIDs and severely reduce any gastrointestinal safety advantages of coxibs. Aspirin should only be co-prescribed if absolutely necessary.

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Background

Since 2000, there have been concerns that coxibs might be associated with an increased risk of serious cardiovascular thrombotic events such as myocardial infarction or stroke. The safety of coxibs and NSAIDs has been kept under continual review by CHM. In 2004, clinical trial evidence confirmed that selective coxibs were associated with a small increased risk of such events, triggering voluntary withdrawal of the drug rofecoxib (Vioxx) and a European-wide review of the remaining selective coxibs. Following this review in 2005, coxibs were contraindicated in patients with established ischaemic heart disease, cerebrovascular disease, and peripheral artery disease. Concerns have been raised that the increased risk of myocardial infarction and stroke identified with coxibs may also apply to non-selective NSAIDs.

Conclusions to date

Evidence continues to suggest that coxibs are associated with an increased thrombotic risk. The risk will vary according to underlying patient risk factors; however, an estimated risk across the whole population may be about three additional events (mainly myocardial infarction) per 1000 patients per year compared with placebo.1,3?5 Dose-related adverse effects may manifest early and the risk may persist throughout treatment.6

A review of the safety of NSAIDs in 2005 concluded that there were inadequate data to update prescribing advice. However, sufficient evidence has now accrued to suggest that some NSAIDs may be associated with a small increased risk of thrombotic events when used at high doses and for long-term treatment,1 that diclofenac has a thrombotic risk profile similar to that of licensed doses of etoricoxib,2 and that naproxen is associated with a lower risk than coxibs.1

Product information for NSAIDs will be updated in due course, and the procedure to begin updating this information is under discussion.

CHM is setting up a cross-specialty expert group to consider all aspects of the risks and benefits of anti-inflammatory and analgesic drugs, and to provide updated advice on the safe use of these products as new evidence emerges.

Questions and answers for patients are attached below, and further information is available at http://www.mhra.gov.uk

Yours sincerely,

Professor Gordon Duff
Chairman, Commission on Human Medicines

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NSAIDs and coxibs—Questions and answers

1. What are NSAIDs?

Non-steroidal anti-inflammatory drugs (commonly known as NSAIDs) are widely used effective medicines for treatment of arthritis and many other painful conditions. There are many medicines in the NSAID class. Most, such as diclofenac (Voltarol) and naproxen (Naprosyn) are available only on prescription, whereas ibuprofen (Nurofen) can also be bought in shops and pharmacies. NSAIDs act by interfering with the body's inflammatory process by blocking enzymes called cyclo-oxygenases (COX-1 and COX-2). NSAIDs vary in their "selectivity" for cyclo-oxygenase enzymes. Selective inhibitors of COX-2 (coxibs) have a more targeted mechanism against COX-2 alone, and for this reason are thought to have fewer side-effects on the gastrointestinal system.

2. What is known about the safety of NSAIDs?

NSAIDs are generally well-tolerated, and most patients do not have side-effects. The most common side-effects are gastrointestinal irritation (eg, abdominal pain, heartburn, nausea, and vomiting). Rarely, serious side-effects such as gastrointestinal ulceration or bleeding may occur, which are more likely with high doses and prolonged use. NSAIDs can also cause allergic reactions, fluid retention, and various other rare side-effects, which are listed in the product information (including patient information leaflets). The cardiovascular risk with non-selective NSAIDs was considered last year by the UK and European expert committees (see http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=227). Since then, further evidence has emerged, which suggests that some NSAIDs may be associated with a small increased risk of thrombotic events (eg, heart attack or stroke) when used at high doses and for a long time.

3. What are selective COX-2 inhibitors?

COX-2 selective inhibitors (commonly known as coxibs) are newer anti-inflammatory medicines developed to produce fewer gastrointestinal side-effects than NSAIDs. Coxibs are also used in the treatment of inflammatory and painful conditions such as arthritis. Available coxibs include celecoxib (Celebrex), etoricoxib (Arcoxia), and lumiracoxib (Prexige), which are taken as tablets, and parecoxib (Dynastat), which is given by injection for short-term pain relief while in hospital.

4. What is known about the safety of coxibs?

Evidence suggests that patients treated with coxibs may be at a small increased risk of arterial thrombotic events such as heart attacks and strokes compared with non-users. In February 2005 the Committee on Safety of Medicines (CSM, which has now been replaced by the Commission on Human Medicines or CHM) advised that coxibs should not be used in patients who have some types of cardiovascular disease. For other patients, doctors were advised to consider carefully in individual patients the potential balance of gastrointestinal benefits in terms of tolerability and cardiovascular risks associated with coxibs.

5. What is the concern about thrombotic reactions with NSAIDs and coxibs? Do they have the same thrombotic risk as each other?

The level of thrombotic risk for NSAIDs and coxibs is small, although it may vary between individual NSAIDs and coxibs. New evidence for the NSAID diclofenac suggests that it has a cardiovascular risk similar to that of at least one coxib—etoricoxib. Updated evidence for another NSAID, called naproxen, suggests this drug is associated with a lower thrombotic risk compared with coxibs; however, further studies of this drug are needed to establish fully its risk profile. Information for ibuprofen (an NSAID) suggests that high doses (2400 mg a day) might be associated with a small increased thrombotic risk, but studies do not suggest that low doses (1200 mg a day or less) are associated with increased risk of heart attack. Further studies are needed to define the thrombotic safety profile of other NSAIDs.

6. What is known about the level of thrombotic risk?

The level of thrombotic risk with NSAIDs and coxibs is small, especially for patients without other risk factors. At present, the exact level of risk for individual coxibs and NSAIDs is not known. Evidence from clinical trials of coxibs suggests that about 3 additional thrombotic events per 1000 patients per year may occur in the general population. In order to minimise risk, healthcare professionals are advised to prescribe the lowest dose for the shortest time to control symptoms.

7. What is diclofenac, and how widely is it used?

Diclofenac is an NSAID that was licensed in November 1978 for treatment of various inflammatory and painful conditions such as arthritis, back pain, and postoperative pain. Between July 1, 2005, and June 30, 2006, approximate usage of diclofenac in general practice was 3·5 million patients; however, more than 80% of patients received three or fewer prescriptions*.

8. What is naproxen, and how widely is it used?

Naproxen is an NSAID that was licensed in April 1973 for treatment of pain and inflammation in conditions such as rheumatic disease, other musculoskeletal disorders, and gout. Approximate usage of naproxen in general practice was 0·5 million patients between July 1, 2005, and June 30, 2006*.

9. What is the new evidence?

New findings from clinical trials have recently become available for the coxibs etoricoxib (see http://www.merck.com/newsroom/press_releases/research_and_development/2006_0823.html),rofecoxib (see http://content.nejm.org/cgi/content/extract/355/2/113),and celecoxib (see http://content.nejm.org/cgi/content/abstract/355/9/873 and http://content.nejm.org/cgi/content/short/355/9/885). Another study combined the results of 138 clinical trials that compared coxibs with placebo or NSAIDs (see http://bmj.bmjjournals.com/cgi/content/full/332/7553/1302), and several recent population-based studies have assessed the risks associated with coxibs and NSAIDs (Jick H and colleagues, *Pharmacotherapy* 2006; **26:** 1379–87; Lewis MA and colleagues, *Pharmacoepidemiol Drug Saf* 2006; **15:** S59; Levesque LE and colleagues, see http://www.cmaj.ca/cgi/content/full/174/11/1563; and McGettigan and Henry, *JAMA* 2006; **296:** E1–E12).

Although substantial new evidence has emerged, it must be remembered that some studies can have limitations because of their methods, the number of participants included, or because of the doses used to compare different treatments. No medicine is without risk, and consideration of the benefits and risks associated with NSAIDs and coxibs is important—particularly with regard to their effects on the cardiovascular and gastrointestinal systems.

10. What about other adverse effects, such as high blood pressure, fluid retention, and heart failure?

All NSAIDs and coxibs can have effects on the kidney, particularly at high doses, which increase the risk of fluid retention, high blood pressure, and (rarely) heart failure in at-risk patients. These risks are described in the patient information leaflet.

11. How might coxibs and NSAIDs increase cardiovascular risk?

The mechanisms by which coxibs might increase thrombotic risk remain uncertain. Several ideas have been proposed, including both direct effects (eg, formation of a blood clot, narrowing of blood vessels, stimulation of fat deposition in arteries, effects on the stability of fatty plaques, impairment of the ability of the heart to tolerate low oxygen concentrations, or impaired growth of new blood vessels), and indirect effects (eg, increased blood pressure and increased blood volume).

12. What is the most up-to-date prescribing advice for NSAIDs and coxibs?

All anti-inflammatory medicines (including NSAIDs and coxibs) should be **used at the lowest possible dose and for the shortest possible period necessary to** control symptoms.

There is no need to stop taking regular NSAID or coxib treatment. There is also no need for patients to switch between NSAIDs: the prescribing of NSAIDs and coxibs should be based on careful consideration of a patient's condition and risk factors for treatment, particularly with regard to the known effects of NSAIDs and coxibs on the gastrointestinal and cardiovascular systems.

13. I've been taking diclofenac regularly for some time. Do I need to change treatment?

Patients who gain effective pain relief by taking diclofenac regularly do not need to switch immediately to another NSAID based on current evidence. At the next routine review, the choice of NSAID can be reviewed as necessary.

14. Is ibuprofen still safe enough to be bought over the counter?

Yes. For doses available over the counter, ibuprofen has an established safety profile, particularly with regard to gastrointestinal adverse effects. Whereas there is some evidence for an increased thrombotic risk associated with prolonged treatment and **high** doses of ibuprofen, short-term use at doses that can be bought over the counter are unlikely to be associated with any significant increase in risk.

15. Should patients take NSAIDs or coxibs together with aspirin, which helps prevent heart attacks and strokes?

Patients should only take NSAIDs or coxibs together with aspirin when absolutely necessary, because such a combination greatly increases the risk of gastrointestinal side-effects. Patients who are unsure about whether or not to take aspirin together with anti-inflammatory treatment should discuss this issue with their doctor or pharmacist at a routine appointment.

16. Do the contraindications of coxibs for people with heart disease, stroke, or peripheral artery disease remain?

The contraindications of coxibs for people with heart disease, stroke, or peripheral artery disease were implemented throughout Europe, and remain in place. The current regulatory position will be reviewed with further data analyses and the emergence of new evidence.

17. What should patients do if they are concerned?

Anyone who is concerned about the potential risks associated with a medicine should discuss the matter with their doctor at a routine appointment, who may reassess a patient to ensure they are taking the most appropriate anti-inflammatory. Such an assessment should consider a patient's need for pain relief and any particular treatment preference they have, as well as any risk factors they may carry.

18. What will happen next?

The Medicines and Healthcare products Regulatory Agency will continue to monitor closely the safety of NSAIDs and coxibs, and will issue advice and information to healthcare professionals and patients accordingly. Product information for NSAIDs will be updated accordingly, and the procedure to begin updating this information is under discussion.

*Data derived from IMS Health Disease Analyzer – Mediplus [Jun 2006] by the MHRA.