From the Chief Medical Officer:
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Department of
Health, Social Services and Public Safety
An Roinn
Sláinte, Seirbhísí Sóisialta agus Sábháilteachta Poiblí
www.dhsspsni.gov.uk

URGENT COMMUNICATION

HSS(MD)26-2005

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- Out of Hours Services; and
- Prescribing Advisers in Primary Care

Medical Directors of HSS Trusts for cascade to:
- All doctors in HSS Trusts

Regional Medicines and Poisons Information Service

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Your Ref:
Our Ref:
Date: 3 August 2005

Dear Colleague

RE: CARDIOVASCULAR SAFETY ON NSAIDs – REVIEW OF EVIDENCE

As part of a European wide review, the Committee on Safety of Medicines has reviewed the cardiovascular safety on non-steroidal anti-inflammatory drugs (NSAIDs). No changes to current prescribing practice are recommended on the basis of currently available evidence. Please find attached to the letter:

1. Advice from Professor Gordon Duff, Chairman of the Committee on Safety of Medicines; and

2. A questions and answers leaflet for patients.

Further information on this topic is available at www.mhra.gov.uk.

Yours sincerely

HENRIETTA CAMPBELL (DR)
CHIEF MEDICAL OFFICER

FRANCIS RICE (MR)
ACTING CHIEF NURSING OFFICER

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CHIEF PHARMACEUTICAL OFFICER

2 August 2005

CARDIOVASCULAR SAFETY OF NSAIDs
REVIEW OF EVIDENCE

Dear Colleague

Following concerns that the increased risk of myocardial infarction (MI) and stroke identified with selective COX-2 inhibitors may also apply to non-selective non-steroidal anti-inflammatory drugs (NSAIDs), the Committee on Safety of Medicines (CSM) has reviewed the available safety data, which mostly relate to ibuprofen, diclofenac and naproxen. The CSM has concluded that the evidence is insufficient to change the balance of risks and benefits of NSAIDs, and no changes to current prescribing practice are recommended on the basis of current evidence on thrombotic risk.

Advice relating to non-selective NSAIDs:

- non-selective NSAIDs are widely used effective medicines in the treatment of arthritis and other painful conditions;
- prescribing should be based on overall safety profiles of NSAIDs (particularly gastrointestinal safety) as set out in product information, and risk factors for individual patients;
- switching treatment between non-selective NSAIDs is not justified on the available evidence;
- all patients should take lowest effective dose of NSAIDs or COX-2 inhibitors for the shortest time necessary to control symptoms.

Advice relating to selective COX-2 inhibitors remains:

- patients with established ischaemic heart disease (IHD), cerebrovascular disease should not take coxibs: celecoxib (Celebrex), etoricoxib (Arcoxia), and parecoxib (Dynastat);
- for patients with risk factors for cardiovascular events, individual risk assessment is appropriate.

Background

Since 2000 there have been concerns that selective COX-2 inhibitors might be associated with an increased risk of serious cardiovascular thrombotic events, such as MI or stroke. This question has been kept under review by CSM. In 2004, clinical trial evidence confirmed that selective COX-2 inhibitors are associated with a small increased risk of such events. This triggered a voluntary withdrawal of the drug rofecoxib (Vioxx) and a European-wide review of the evidence for the remaining members of the selective COX-2 inhibitor class. The contraindication for selective COX-2 inhibitors in established IHD and cerebrovascular disease was communicated to healthcare professionals in December 2004 and February 2005. Valdecoxib was subsequently withdrawn (April 2005) because of concerns over serious skin reactions. Concerns have been raised that the increased risk of myocardial infarction (MI) and stroke identified with selective COX-2 inhibitors may also apply to non-selective NSAIDs.

Available evidence relating to cardiovascular safety of NSAIDs

Across Europe, the most recent assessment has concentrated on all data sources relating to the cardiovascular safety of a number of widely prescribed NSAIDs: ibuprofen, naproxen, diclofenac, meloxicam, etodolac, nimesulide (not marketed in the UK), nabumetone, indometacin, and ketoprofen. Most data related to ibuprofen, diclofenac and naproxen, including large clinical trials comparing these products to ‘coxibs’ and a substantial number of epidemiological studies. Other evidence has come from basic pharmacology and from spontaneous adverse drug reaction reports. For products other than naproxen, ibuprofen and diclofenac there were insufficient data to allow meaningful assessment of the possible thrombotic risks. The available data have important limitations, and the absence or paucity of evidence should not be taken as meaning that there is a lack of risk with other NSAIDs. More studies are needed to understand and adequately quantify these potential effects. A summary of the evidence is available on the MHRA website (see link below).

Conclusions on cardiovascular risks so far

The available evidence suggests that selective COX-2 inhibitors, as a class, cause a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) compared with placebo, and the risk may increase with dose and duration of exposure.

The evidence available does not permit firm conclusions regarding the cardiovascular safety of naproxen, ibuprofen and diclofenac relative to one another or selective COX-2 inhibitors. There is some evidence that naproxen may have a lower thrombotic risk than selective COX-2 inhibitors, however, this is less clear for ibuprofen and diclofenac. Any cardiovascular risk of non-selective NSAIDs is likely to be small and associated with continuous long-term treatment and higher doses.

Over the Counter (OTC) ibuprofen
At the doses in OTC medicines, ibuprofen has an excellent safety record, particularly in respect of gastrointestinal adverse effects. Whilst evidence relating to any cardiovascular risk associated with prolonged treatment and high doses of ibuprofen is not entirely clear, short-term use at the doses that can be bought over the counter is unlikely to be associated with any measurable increased risk.

Questions and answers for patients and further information appears below and is available at www.mhra.gov.uk .

Yours sincerely

Professor Gordon Duff
Chairman of the Committee on Safety of Medicines

Questions and Answers for patients

1. What are NSAIDs?

Non-steroidal anti-inflammatory drugs (commonly known as 'NSAIDs') are widely used and effective medicines in the treatment of arthritis and many other painful conditions. There are many medicines in the NSAID class. Most, like diclofenac (Voltarol) and naproxen (Naprosyn) are available only on prescription, whilst ibuprofen (Nurofen) can also be bought in shops and pharmacies.

2. What is known about the safety of NSAIDs?

NSAIDs are generally well-tolerated and most patients do not suffer side effects. The most commonly reported side effects are those relating to gastrointestinal irritation, such as abdominal pain, heartburn, nausea and vomiting. Rarely, serious side effects such as gastrointestinal ulceration or bleeding may occur, and this is more likely with high doses and prolonged use of NSAIDs. NSAIDs can also cause allergic reactions, fluid retention and a range of other rare side effects, which are listed in product information including patient information leaflets.

3. What are selective COX-2 inhibitors?

COX-2 selective inhibitors (commonly known as 'coxibs') are newer anti-inflammatory medicines which are thought to produce less in the way of gastrointestinal side effects than NSAIDs. Available coxibs include celecoxib (Celebrex), etoricoxib (Arcoxia) and parecoxib (Dynastat) which is given by injection for short-term use in hospitals.

Recent evidence indicates that patients treated with coxibs may be at a slightly increased risk of heart attacks and strokes. For this reason in February 2005 the Committee on Safety of Medicines (CSM) advised that they should not be used in patients who already have these conditions. For other patients, doctors were advised of the need to carefully consider the potential balance of gastrointestinal and cardiovascular risks of using coxibs on an individual basis.

4. What is the concern about cardiovascular reactions with NSAIDs? Do they have the same cardiovascular risk as COX-2 inhibitors?

From what is known about the actions of these medicines we would expect less cardiovascular risk with non-selective NSAIDs than with COX-2 inhibitors. Levels of risk may vary for individual medicines but current evidence is insufficient to be sure about this. In fact, there is some evidence that naproxen has less cardiovascular risk than coxibs but the evidence for diclofenac and ibuprofen is insufficient and sometimes conflicting. For all other NSAIDs, there is even less evidence at the moment, and this does not support a definitive evaluation of the risks.

5. In view of the varying levels of evidence, what can be concluded?

Any cardiovascular risk caused by the NSAIDs is likely to be small and associated with long-term use at higher doses. For this reason, all anti-inflammatory medicines (including the NSAIDs and coxibs) should be **used at the lowest possible dose and for the shortest possible period necessary to** control symptoms.

The Medicines and Healthcare products Regulatory Agency (MHRA) will continue to carefully review any new evidence to emerge on the safety of NSAIDs and will seek advice from the Committee on Safety of Medicines (CSM) as needed. Some further clinical trial evidence relating to diclofenac is expected within the next 12 months. Other trials may be needed before there is a full understanding of the comparative cardiovascular safety of NSAIDs and coxibs.

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

Yes. In the doses available over the counter, ibuprofen has an excellent safety record, particularly in respect of the risk of gastrointestinal adverse effects. Whilst evidence relating to any cardiovascular risk associated with prolonged treatment and high doses of ibuprofen is not entirely clear, short-term use at the doses which can be bought over the counter is unlikely to be associated with any measurable increase in risk.

7. Is it true that ibuprofen can reduce the effectiveness of low-dose aspirin, taken to prevent heart attacks and strokes?

While this is possible in theory, it has not been shown to occur in practice. Patients should take NSAIDS, such as ibuprofen, together with aspirin only when absolutely necessary, as such a combination increases the risk of gastrointestinal side effects. Any patient who is unsure about whether or not take aspirin together with an NSAID should discuss this with his or her doctor or pharmacist at a routine appointment.

8. What about other 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 have been understood for a long time and are described in the patient information leaflet.

9. What advice has the CSM given to prescribers and patients about the use of NSAIDs in relation to the risk of heart attacks and strokes?

Following a recent detailed review of all available evidence, the CSM emphasised that no changes to current prescribing practice are recommended.

Advice relating to non-selective NSAIDs:

- non-selective NSAIDs are widely used effective medicines in the treatment of arthritis and other painful conditions;
- prescribing should be based on overall safety profiles of NSAIDs (particularly gastrointestinal safety) as set out in product information, and individual risk factors;
- switching treatment between non-selective NSAIDs is not justified on available evidence;
- all patients should take lowest effective dose of NSAIDs or COX-2 inhibitors for shortest time necessary to control symptoms.

Advice relating to Coxibs remains:

- patients with established ischaemic heart disease (IHD), cerebrovascular disease should not take coxibs: celecoxib (Celebrex), etoricoxib (Arcoxia) and parecoxib (Dynastat);
- for patients with risk factors for cardiovascular events, individual risk assessment is appropriate.

10. What should patients do if they are concerned?

There is no need for patients to change their treatment in light of this review. Anyone who is concerned about their medicine should discuss the matter with their pharmacist or doctor at a routine appointment.