

From the Chief Medical Officer:
Dr Henrietta Campbell CB



Department of
**Health, Social Services
and Public Safety**

An Roinn
**Sláinte, Seirbhísí Sóisialta
agus Sábháilteachta Poiblí**

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URGENT COMMUNICATION

HSS(MD)43-2004

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prescribing nurses, practice nurses and sessional doctors
Community Pharmacists
Directors of Primary Care in HSS Boards – for cascade to local
OOH Services
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Your Ref:
Our Ref:
Date: 21 December 2004

Dear Colleague

**ADVICE ON THE USE OF CELECOXIB AND OTHER SELECTIVE COX-2
INHIBITORS IN LIGHT OF CONCERNS ABOUT CARDIOVASCULAR SAFETY**

Attached is a letter from Professor Gordon Duff, Chairman of the Committee on Safety of Medicines. This letter provides interim guidance on the prescribing of all COX-2 inhibitors, in light of emerging evidence. Patients receiving treatment with celecoxib (Celebrex) or other selective COX-2 inhibitors should be advised to make a non-urgent appointment with their GP to have their treatment reviewed in accordance with this guidance.

Also included in this urgent communication is a Question and Answer document which will be useful to inform discussions between practitioners and patients.

Yours sincerely

HENRIETTA CAMPBELL (DR)
CHIEF MEDICAL OFFICER

JUDITH HILL (MISS)
CHIEF NURSING OFFICER

NORMAN MORROW (DR)
CHIEF PHARMACEUTICAL OFFICER

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ADVICE ON THE USE OF CELECOXIB AND OTHER SELECTIVE COX-2 INHIBITORS IN LIGHT OF CONCERNS ABOUT CARDIOVASCULAR SAFETY

Dear Colleague

The Medicines and Healthcare products Regulatory Agency (MHRA) is aware that new data from a clinical trial in the United States has indicated an increased cardiovascular risk (including heart attack and stroke) following treatment with celecoxib (Celebrex). The MHRA has not yet received the data from the clinical trial in question and only has access to the information in the public domain. This letter provides interim advice on prescribing of all COX-2 inhibitors, in light of emerging evidence. Definitive advice will be issued, once further information is available and has been evaluated.

New Advice for Prescribers

- **Patients treated with any COX-2 inhibitor who have established ischaemic heart disease or cerebrovascular disease should be switched to alternative (non-COX-2 selective) treatments as soon as is convenient.**
- **For all patients, alternative treatments should be considered in light of an individual assessment of risks and benefits of COX-2 inhibitors, in particular cardiovascular, gastrointestinal and other risk factors.**
- **Prescribers are reminded that for all NSAIDs (including COX-2 inhibitors), the lowest effective dose should be used, for the shortest duration necessary.**
- **For patients switched to chronic non-selective NSAIDs, consideration should be given to the possible need for gastro-protective treatments.**

Background

Celecoxib is a widely used COX-2 anti-inflammatory, licensed for the treatment of osteoarthritis and rheumatoid arthritis. In the UK approximately 600,000 patients are taking celecoxib. The drug substance is also licensed for the treatment of the rare bowel condition Familial Adenomatous Polyposis (FAP), under the brand name Onsenal.

The cardiovascular safety of COX-2 inhibitors has been continually reviewed by the Committee on Safety of Medicines (CSM) since 2000, following concerns over rofecoxib, which was subsequently withdrawn in September 2004. Product information for celecoxib and other COX-2 inhibitors already includes advice on the need for caution in patients at high risk of cardiovascular events.

The recent letter to healthcare professionals from Pfizer, which highlighted the cardiovascular safety of celecoxib was not authorised by the MHRA.

New Data

The MHRA has not yet received the data from the clinical trial in question and only has access to the information in the public domain.

The study, conducted by the US National Cancer Institute (NCI), the Adenoma Prevention with Celecoxib trial (APC), seemingly involved 2,400 patients with an average duration of 33 months treatment, taking 400 mg or 800 mg celecoxib per day. The risk of major fatal or non-fatal cardiovascular events (including acute myocardial infarction and stroke) was apparently 2.5 times higher than placebo at 400mg and 3.4 times higher with the 800mg dose. The NCI data safety and monitoring board, which is independent of Pfizer, stopped this trial on 17 December 2004.

A separate trial sponsored by Pfizer (Prevention of Spontaneous Adenoma Polyps (PreSAP) trial), does not appear to confirm this risk. This trial has also now been stopped based on the results of the APC trial. No further details are available on this trial at present.

What action should patients take?

Patients receiving treatment with celecoxib (Celebrex) or other selective COX-2 inhibitors should make a non-urgent appointment to have their treatment reviewed. Patients who are concerned prior to their appointment may be advised that there are no harmful effects of stopping selective COX-2 inhibitors, although alternative treatment is likely to be needed to control their symptoms.

If you have any enquiries, please contact the MHRA (medicines) on 020-7084 2000 or e-mail info@mhra.gsi.gov.uk.

Yours sincerely

Prof. Gordon Duff
Chairman
Committee on Safety of Medicines

Celecoxib Questions and Answers

1. What is Celecoxib?

Celecoxib is a widely used COX-2 anti-inflammatory, licensed for the treatment of osteoarthritis and rheumatoid arthritis. The drug substance is also licensed for the treatment of the rare bowel condition Familial Adenomatous Polyposis (FAP), under the brand name Onsenal.

2. How many people in the UK are taking celecoxib?

In the UK approximately 600,000 patients are taking celecoxib

3. What are COX-2 inhibitors?

Anti-inflammatory medicines have been available for many years and are important in the treatment of arthritis and many other painful conditions. One disadvantage of anti-inflammatory medicines is their potential to cause stomach and gut (gastro-intestinal) side effects, which in rare cases can be serious (e.g. ulcers and bleeding). COX-2 selective inhibitors are a relatively new type of anti-inflammatory medicine which are thought to produce less in the way of gastrointestinal side effects than older 'non-selective' drugs.

4. What new advice is the MHRA and CSM issuing today?

The Chairman of the Committee on Safety of Medicines, has today issued a letter with the following advice for prescribers:

- Patients treated with any COX-2 inhibitor who have established ischaemic heart disease or cerebrovascular disease should be switched to alternative (non-COX-2 selective) treatments as soon as is convenient.
- For all patients, alternative treatments should be considered in light of an individual assessment of risks and benefits of COX-2 inhibitors, in particular cardiovascular, gastrointestinal and other risk factors.
- Prescribers are reminded that for all NSAIDs (including COX-2 inhibitors), the lowest effective dose should be used, for the shortest duration necessary.
- For patients switched to chronic non-selective NSAIDs, consideration should be given to the possible need for gastro-protective treatments.

5. Why has this new advice been issued?

The new advice has been issued in light of emerging evidence over the cardiovascular safety of celecoxib and of COX-2 inhibitors, as a class of drugs. The Medicines and Healthcare products Regulatory Agency (MHRA) is aware that new data from a clinical trial the United States has indicated an increased cardiovascular risk (including heart attack and stroke) following treatment with celecoxib (Celebrex). The MHRA has not yet received the data from the clinical trial in question and only has access to the information in the public domain. However, the MHRA and CSM have today issued interim advice regarding COX-2 inhibitors, in light of the cardiovascular safety concerns that may exist across the whole class.

6. What is the new evidence of risk with celecoxib?

The MHRA has not yet received the data from the clinical trial in question and only has access to the information in the public domain. The study, conducted by the US National Cancer Institute (NCI), the Adenoma Prevention with Celecoxib trial (ACP), seemingly involved 2,400 patients with an average duration of 33 months treatment, taking 400 mg or 800 mg celecoxib per day. The risk of major fatal or non-fatal cardiovascular events (including acute

myocardial infarction and stroke) was apparently 2.5 fold higher than placebo at 400mg and 3.4 times higher with the 800mg dose. The NCI Data Safety and Monitoring Board, which is independent of Pfizer, stopped this trial on 16 December 2004.

7. Hasn't a second trial also been stopped?

A separate trial sponsored by Pfizer (Prevention of Spontaneous Adenoma Polyps (PreSAP) trial), does not appear to confirm this risk. This trial has also now been stopped based on the results of the APC trial. No further details are available on this trial at present.

8. When will further information or advice be available?

The MHRA has urgently requested the relevant clinical trial data from the company. Once this is available and has been evaluated, definitive advice will be issued.

9. Does the same advice apply to all COX-2 inhibitors?

Although the latest data only relate to celecoxib, similar concerns led to the withdrawal of rofecoxib and it is plausible that the same risks of stroke and heart attack relate to all selective COX-2 inhibitors. For this reason, as a precaution, the MHRA and CSM are issuing advice that relates to all members of the class.

10. What should patients do?

Patients receiving treatment with celecoxib (Celebrex) or other selective COX-2 inhibitors should make a non-urgent appointment to have their treatment reviewed. Patients who are concerned prior to their routine appointment may be advised that there are no harmful effects of stopping selective COX-2 inhibitors, although alternative treatment is likely to be needed to control their symptoms.

11. What alternative treatments are there?

COX-2 inhibitors are used to treat arthritic conditions, such as osteoarthritis and rheumatoid arthritis and some are also licensed for the treatment of acutely painful conditions. There are many other alternative painkilling and anti-inflammatory medicines available. For some patients with mild symptoms, simple painkillers like paracetamol may be sufficient. For others, there are many traditional anti-inflammatory medicines, including ibuprofen (which is available over the counter), diclofenac, naproxen and indomethacin. Pharmacists will be able to provide initial advice.

12. Aren't patients being switched to other anti-inflammatories likely to be at risk of gastrointestinal problems, such as ulcers?

The traditional NSAIDs are thought to carry a higher risk of stomach and gut (gastrointestinal) problems than the COX-2 inhibitors. However, it seems likely that COX-2 inhibitors carry a risk of adverse effects in terms of heart attack and stroke. Therefore the risks and benefits need to be weighed for the individual patient depending on their risk factors. Prescribers may also consider the use of protective treatment for the stomach, when switching patients to traditional anti-inflammatories.

13. I've been on a COX-2 for a long time – will there be long-term harm?

There is no evidence that the increased risk of heart attack or stroke persists after treatment with COX-2 inhibitors has stopped.

14. I am on a COX-2 inhibitor and have had heart problems or a stroke in the past – what should I do?

You should make a non-urgent appointment to see your GP, who will review your medication and recommend alternative treatment. Stopping COX-2 treatment will not cause any harm, but you are likely to need alternative treatment to control your symptoms.