

Medical & Allied Branch

**URGENT COMMUNICATION**

**HSS(MD)9-2005**

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Your Ref:  
Our Ref:  
Date: 21 February 2005

Dear Colleague

**RE: UPDATED ADVICE ON THE SAFETY OF SELECTIVE COX-2 INHIBITORS**

Enclosed is updated advice on the safety of selective COX-2 inhibitors, together with a Questions and Answers leaflet for patients taking these medicines.

This advice on the safety of COX-2 inhibitors follows a European wide review of the cardiovascular data. It updates the information provided by the Committee on Safety of Medicines in December 2004. The evidence suggests that selective COX-2 inhibitors, as a class, may cause an increase risk of thrombotic events (eg myocardial infarction and stroke) compared with placebo and some NSAIDs, and the risk may increase with dose and duration of exposure.

Yours sincerely

**HENRIETTA CAMPBELL (DR)**  
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: This letter is available at [www.dhsspsni.gov.uk](http://www.dhsspsni.gov.uk) and also on the DHSSPS Extranet  
: which can be accessed directly at <http://extranet.dhsspsni.gov.uk> or by going through  
: the HPSS Web at <http://www.n-i.nhs.uk> and clicking on DHSSPS.  
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Date: 17<sup>th</sup> February 2005  
Reference: CEM/CMO/2005/4

## UPDATED ADVICE ON THE SAFETY OF SELECTIVE COX-2 INHIBITORS

Dear Colleague

I am writing to update you on the safety of COX-2 inhibitors following a European- wide review of the cardiovascular data. The evidence suggests that selective COX-2 inhibitors, as a class, may cause an increased risk of thrombotic events (e.g. myocardial infarction and stroke) compared with placebo and some NSAIDs, and the risk may increase with dose and duration of exposure. It is not possible to quantify the risk precisely, but it is considered unlikely to exceed one extra serious thrombotic event per 100 patient years, over the rate for no treatment. There are no major changes to existing advice, our earlier advice has been reinforced as follows.

### Summary of Updated advice for all Selective COX-2 inhibitors (celecoxib, etoricoxib, valdecoxib and parecoxib)

- **Patients with established ischaemic heart disease or cerebrovascular disease should be switched to alternative treatment:** in addition, the existing contraindication for severe heart failure is now extended to include moderate heart failure NHYA class II-IV).
- **For all patients the balance of gastrointestinal and cardiovascular risk should be considered before prescribing a COX-2 inhibitor,** particularly for those with risk factors for heart disease and those taking low dose aspirin, for whom gastrointestinal benefit has not been clearly demonstrated.
- **The lowest effective dose of COX-2 inhibitor should be used for the shortest necessary period.** Periodic re-evaluation is recommended, especially for osteoarthritis patients who may only require intermittent treatment.
- **Gastroprotective agents should be considered for patients switched to non-selective NSAIDs.**

### New advice for etoricoxib

Etoricoxib may be associated with more frequent and severe effects on blood pressure than some other COX-2 inhibitors and NSAIDs, particularly at high doses.

- **Etoricoxib treatment should not be initiated in patients whose hypertension is not under control.**
- **Careful monitoring of blood pressure is advised for patients taking etoricoxib.**

### Reminder on Valdecoxib/Parecoxib

Prescribers are reminded that valdecoxib and parecoxib may be associated with higher rates of serious skin reactions (e.g. Stevens-Johnson syndrome, Toxic Epidermal Necrolysis) than other COX-2 inhibitors. Treatment should be stopped at the first signs of skin rash or hypersensitivity reaction.

### Background

In 2004, data from a number of clinical trials involving rofecoxib, celecoxib and valdecoxib/parecoxib suggested a pattern of increased cardiovascular risk. Rofecoxib was withdrawn from the market in September 2004, and CSM issued precautionary advice for the use of all COX-2 inhibitors in December 2004 following new clinical trial data relating to celecoxib. This advice has now been confirmed and updated by review of the available evidence of cardiovascular safety. Product information for COX-2 inhibitors is being updated.

The overall risks and benefits of selective COX-2 inhibitors continue to be closely reviewed as new data emerge, and the CSM will provide further advice as necessary. Please report suspected adverse drug reactions to the MHRA and CSM using the Yellow Card Scheme. We are currently piloting direct patient reporting through the Yellow Card Scheme website at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk) and using paper-based Patient Yellow Card report forms. Patients may contact the MHRA if they would like a form (send an email to [patientreporting@mhra.gsi.gov.uk](mailto:patientreporting@mhra.gsi.gov.uk) or telephone - (+44) 020 7084 2101). A set of questions and answers for patients is attached.

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

Yours sincerely

Prof. Gordon Duff  
Chairman  
Committee on Safety of Medicines

## **Questions and Answers for patients taking COX-2 inhibitors**

### **1. Which medicines are selective COX-2 inhibitors?**

The following are selective COX-2 inhibitors: celecoxib (Celebrex), etoricoxib (Arcoxia), valdecoxib (Bextra) and parecoxib (Dynastat).

### **2. What is the risk with Selective COX-2 inhibitors?**

Selective COX-2 inhibitors are effective anti-inflammatory medicines suitable for the treatment of arthritis and, in some cases, other painful conditions. They are thought to cause less irritation of the gastrointestinal tract (stomach, gut) than other anti-inflammatory medicines, but may be associated with a slightly greater risk of heart attacks and strokes. It is not possible to measure the risk precisely from the available evidence, but these medicines are unlikely to cause more than one extra heart attack or stroke per 100 patients treated for a year, over the normal risk (if you don't take any treatment).

In general, if a COX-2 inhibitor is suitable in your case, your doctor will prescribe the lowest effective dose for the shortest time necessary to control your symptoms. This is important as the risks may increase with use of high doses and prolonged treatment.

### **3. 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.

### **4. I am on a COX-2 inhibitor and believe I am at risk of heart disease (e.g. I have high blood pressure, high cholesterol, diabetes, or am a smoker) - what should I do?**

You do not need to stop treatment, but you should discuss your treatment with your doctor at your next routine appointment. Your doctor will consider whether it would be better to continue with the medicine or change to another type of treatment, depending on your overall cardiovascular (heart, blood vessel) risks and risks of suffering gastrointestinal (stomach, gut) problems.

### **5. Is it OK to take aspirin for the prevention of heart disease/stroke/mini-stroke (TIA) while I am on a COX-2 inhibitor**

If you are taking aspirin because you have already been diagnosed as having a stroke, mini-stroke or heart disease, you should make a non-urgent appointment to see your doctor, 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.

If you have not been diagnosed as having a stroke, mini-stroke or heart disease, then you should discuss your treatment with your doctor at your next routine appointment. Your doctor will consider whether it would be better to continue with the medicine or change to another type of treatment, depending on your overall cardiovascular (heart, blood vessel) risks, and risks of suffering gastrointestinal (stomach, gut) problems.

### **6. I have not had heart problems or a stroke in the past and I don't think I'm at particular risk of these problems. Can I go on taking COX-2 inhibitor treatment?**

You do not need to stop treatment, but if you're worried, you may wish to discuss your treatment with your pharmacist. Your doctor may have prescribed the medicine because you have had gastrointestinal (stomach/gut) problems and other types of anti-inflammatory medicines may be less suitable in your case.

**7. For how long is it safe to take a COX-2 inhibitor?**

It is possible that prolonged treatment for many months or years may have higher risks and your doctor will therefore reassess regularly your need for treatment. It is not possible to provide estimates of risk for different lengths of time of treatment, based on the available evidence. It is best to use the lowest dose for the shortest time necessary, and to have periodic review of your medication.

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

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

**9. I am taking etoricoxib (Arcoxia) and I've heard that this medicine can cause high blood pressure. What do I need to do?**

There is no need for you to stop taking your treatment, but you should make a non-urgent appointment with your General Practice Nurse to have your blood pressure checked.