Primary and Community Care Directorate
Pharmacy Division

T: 0131-244 2528 F: 0131-244 2375
E: irene.foster@scotland.gsi.gov.uk
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The Scottish Government

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

LUMIRACOXIB – SUSPENSION OF UK LICENCES WITH IMMEDIATE EFFECT (NON URGENT) CASCADE WITHIN 48 HOURS

Please see attached for onward transmission a copy of a message from Professor Gordon Duff, Chairman, Commission on Human Medicines about the suspension of UK licences (marketing authorisations) due to the risk of severe liver reactions associated with lumiracoxib.

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

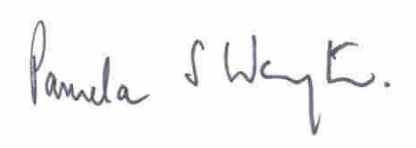
- All General Practitioners - please ensure this message is seen by all practice nurses and non principals working in your practice and retain a copy in your 'locum information pack'.
- Deptutising services

Please could all Directors of Public Health forward the message to:

- Chief Executives NHS Boards

Specialists in Pharmaceutical Public Health/Directors of Pharmacy will also receive this information through the usual drug alert channels to forward on to community pharmacists.

Yours sincerely



PAMELA WARRINGTON
Deputy Chief Pharmaceutical Officer

Ref: EL(07)A/21

LUMIRACOXIB - SUSPENSION OF UK LICENCES WITH IMMEDIATE EFFECT

19 November 2007

Dear Colleague,

I am writing to inform you that the UK licences (marketing authorisations) for lumiracoxib have been suspended and stocks are being withdrawn from pharmacies, on the basis of advice from the Commission on Human Medicines (CHM). Accordingly, no further prescriptions of lumiracoxib should be written, and patients should be reviewed to discuss alternative anti-inflammatory treatment at the next convenient opportunity.

Risk of severe liver reactions with lumiracoxib

On the basis of recent adverse drug reaction (ADR) reports, CHM has advised that lumiracoxib is associated with a risk of severe, potentially life-threatening hepatotoxicity that appears greater than for a number of other authorised non-steroidal anti-inflammatory drugs.

In reaching this advice, CHM has noted that although there is some evidence that the risk of hepatotoxicity may be related to dose and duration of exposure, cases of serious hepatotoxicity have been identified following exposure to the licensed 100mg dose, and after short duration of treatment (less than one month in some cases). CHM therefore concluded that recently introduced risk minimisation measures (baseline and monthly liver function test monitoring, and contraindications for patients with current or previous hepatic dysfunction) cannot be relied upon to guarantee patient safety, and further restrictions are unlikely to be practical.

Further Europe-wide review

Whilst the marketing authorisations are suspended there will be a full regulatory review of the risks and benefits of lumiracoxib within Europe, and further advice will be issued as necessary.

Switching patients to alternative treatments

Patients should be invited to make an appointment with their GP as soon as convenient, to discuss switching to an alternative treatment. Ideally, patients should stop taking lumiracoxib straight-away (especially if they have any symptoms of systemic illness), but it would be acceptable to continue treatment until the next convenient appointment if they are well and gaining important symptomatic relief from this medicine.

In selecting alternative anti-inflammatory treatment for hip or knee osteoarthritis, the balance of risks and benefits of each treatment should be considered alongside individual patient history and preferences. Available options include other licensed 'coxibs' (celecoxib and etoricoxib), and other non-steroidal anti-inflammatory agents (e.g. ibuprofen and naproxen). The possible need for gastroprotective agents (such as proton pump inhibitors) should be considered.

Information for patients

The attached list of questions and answers includes specific advice for patients (see questions 10 – 12).

Reporting suspected adverse drug reactions

It remains important to report all suspected ADRs in relation to lumiracoxib. Any new ADR reports will be considered in the forthcoming Europe-wide review. Please report using a Yellow Card or at www.yellowcard.gov.uk.

For further information please contact the Medicines and Healthcare products Regulatory Agency (MHRA) at 020 7084 2000 (www.mhra.gov.uk).

Professor Sir Gordon Duff
Chairman, Commission on Human Medicines

General questions and answers

1. What is lumiracoxib?

Lumiracoxib (Prexige) is used to treat painful symptoms of osteoarthritis of the knee and hip; the licensed dose in the EU is 100mg daily. It is one of a class of products called Cox-2 selective inhibitors ('coxibs'), which are a relatively new type of anti-inflammatory medicine thought to produce fewer gastrointestinal side effects than older non-selective 'non-steroidal anti-inflammatory drugs' (NSAIDs). Available coxibs include celecoxib (Celebrex), etoricoxib (Arcoxia), and parecoxib (Dynastat – which is given by injection for short-term use in hospitals). Available non-selective NSAIDS include ibuprofen (Brufen, Nurofen), naproxen (Naprosyn), diclofenac (Voltarol), etodolac (Lodine), meloxicam (Mobic) and others.

2. Where is lumiracoxib currently licensed, and what actions have been taken by other regulatory authorities in relation to liver safety concerns?

Lumiracoxib has been approved in more than 50 countries worldwide. Since its first launch in Brazil on 01 July 2005, lumiracoxib has been marketed in 30 countries worldwide, including 9 countries in the EU.

On 10 Aug 2007 Australia withdrew the marketing authorisation due to hepatic safety concerns based on reports of liver failure, and soon after that, New Zealand withdrew the marketing authorisation for 200 mg and 400 mg tablets (but kept the licences of 100 mg once daily for osteoarthritis with additional restrictions on use). Turkey suspended the marketing authorisation for 100mg pending further review. In September, the Food and Drug Administration in the United States issued a 'non-approvable' letter for lumiracoxib 100mg, and in October, Canada withdrew the marketing authorisation for 100mg and Aruba withdrew the product licenses for 100mg, 200mg and 400mg.

3. Why is lumiracoxib being withdrawn?

The Commission on Human Medicines (CHM) has reviewed the most recent evidence on the safety of lumiracoxib, in particular relating to liver adverse reactions. CHM has advised that urgent action is required to protect public health, and that suspension of the marketing and use of lumiracoxib is warranted. The latest evidence on cases of serious hepatotoxicity includes several new cases reported with the 100mg daily dose (licensed in the EU). In some cases, serious hepatotoxicity occurred after less than 1 month of treatment.

4. How many suspected adverse hepatic reactions have been reported in association with lumiracoxib?

Worldwide, up to 26 October 2007 there have been 159 spontaneous reports of suspected adverse liver reactions to lumiracoxib of which 91 were considered serious and 68 considered non-serious by the reporter. Two of these suspected adverse hepatic reactions had a fatal outcome.

Up to 13 November 2007, we have received 23 reports of suspected adverse reactions to lumiracoxib in the UK since March 2006 through the Yellow Card Scheme. Three of these were liver reactions (detected by blood tests). None

of these reactions were said to have been severe* but 2 were considered serious by the reporter with the remaining case involving patient hospitalisation. We have not received any reports of fatal adverse reactions to lumiracoxib in the UK.

It is important to note that not all adverse drug reactions are reported and therefore these data cannot be used to calculate the frequency of adverse reactions. In addition, a report of a suspected adverse reaction does not necessarily mean that it was caused by the drug. Factors such as other medicines taken at the same time or the patient's underlying condition may have contributed towards or caused the adverse events.

*The definition of severe is hepatic failure or "Hy's case" (transaminases > 3ULN and bilirubin >2ULN) or a fatal outcome or liver transplantation.

5. How many severe* liver reactions have been reported worldwide?
Worldwide (up to 31 October), there have been 20 case reports of severe* liver reactions suspected to be at least possibly related to use of lumiracoxib, including 14 cases of liver failure. Two cases had a fatal outcome and in 3 cases, patients required a liver transplant. Of the 9 severe* cases related to use of the 100mg dose, 1 resulted in liver transplant.

It is important to remember that just because a suspected reaction has been reported it does not necessarily mean that the drug was responsible for the event. Other factors, such as underlying disease or other drugs may also have contributed towards or caused the reaction.

*The definition of severe is hepatic failure or "Hy's case" (transaminases > 3ULN and bilirubin >2ULN) or a fatal outcome or liver transplantation.

6. How many people have used lumiracoxib?
Approximately 8.5 million prescriptions of lumiracoxib have been written worldwide since launch in July 2005. In the UK approximately 5,000 patients have received one or more prescriptions for lumiracoxib in the year October 2006 – September 2007.

7. What alternative treatments are there?
There is a range of alternative anti-inflammatory medicines that are licensed for the symptomatic relief of osteoarthritis. Options include other licensed 'coxibs' (celecoxib and etoricoxib), and traditional non-steroidal anti-inflammatory agents (e.g. ibuprofen and naproxen).

In selecting alternative anti-inflammatory treatment for hip or knee osteoarthritis, the balance of risks and benefits of each treatment should be considered alongside individual patient history and preferences. The possible need for gastroprotective agents (such as proton pump inhibitors) should be considered.

8. Will lumiracoxib ever be available again?
Whilst the marketing authorisations are suspended there will be a European-wide review of the risks and benefits of treatment. Further advice will be issued when the review has concluded.

9. What regulatory actions are being taken by other countries in the European Union?
Each country will make its own decision on immediate action. Ultimately, a further Europe-wide review of the risks and benefits of treatment will be conducted. Further advice will be issued when the review has concluded.

Questions and answers for patients

10. I am taking lumiracoxib, what should I do?
You should make an appointment with your doctor as soon as convenient, to discuss switching to alternative treatment. Any unused lumiracoxib tablets should be returned to the pharmacist or GP for disposal.

11. Can I continue to take the lumiracoxib (Prexige) tablets that I have before I see the doctor?

If you are feeling unwell, for example if you feel sick, have vomiting, loss of appetite, tiredness, stomach pains, dark urine or itching or yellowing of the skin [jaundice], you should stop taking lumiracoxib and see you doctor immediately.

If you are generally well and your arthritis pain is not too bad then it would be ideal to stop taking lumiracoxib straight away, and then see your doctor at a convenient time in the next few days (in the meantime you could consider paracetamol as an alternative). However, if lumiracoxib (Prexige) is providing important relief from your arthritis it would be alright to continue to take the medicine until you see the doctor.

12. I have taken lumiracoxib in the past – am I at risk of a liver reaction now?
In most cases, patients who had adverse liver reactions experienced them during treatment with lumiracoxib. There is no need to be concerned if you are feeling well, however if you feel unwell (for example, you feel sick, have vomiting, loss of appetite, tiredness, stomach pains, dark urine, or itching or yellowing of the skin [jaundice]), you should contact your doctor who may arrange for you to have a precautionary blood test.