European Medicines Agency
Press office

London, 27 June 2005
Doc. Ref. EMEA/210745/2005 corr

Questions and Answers on COX-2 Inhibitors

1. What action has the EMEA taken?

After reviewing all available data on cardiovascular safety and serious skin reactions associated with the use of COX-2 inhibitors, the European Medicines Agency (EMEA) has recommended the suspension of the marketing authorisation for **Bextra** (valdecoxib) and recommended new warnings and contraindications for other COX-2 inhibitors that continue to be available in the European Union (EU).

The Agency's Committee for Medicinal Products for Human Use (CHMP) said that additional warnings and contraindications are necessary for all COX-2 inhibitors due to the cardiovascular risks, but concluded that the additional risks of serious and potentially fatal skin reactions associated with the use of Bextra outweigh its benefits. The suspension of Bextra will be reviewed within one year, during which time Pfizer has the opportunity to provide further safety and other relevant data before the Committee can consider the re-introduction of the product in the European Union. At the request of the EMEA, Pfizer voluntarily agreed in April 2005 to withdraw the product from the market in the EU.

2. Why has the EMEA reviewed COX-2 inhibitors?

Concerns have been raised regarding an increased risk of cardiovascular events (including heart attack and stroke) for the class of COX-2 inhibitors. In November 2004, the EMEA began a Europe-wide review of COX-2 inhibitors at the request of the European Commission. This review was broadened in April 2005 to include assessment of serious skin reactions occurring with COX-2 inhibitors, following the voluntary withdrawal of Bextra by the marketing authorisation holder.

3. What are COX-2 inhibitors ?

COX-2 selective inhibitors are a relatively new type of non-steroidal anti-inflammatory drugs (NSAIDs) that are considered to produce fewer gastro-intestinal side effects than older "non-selective" drugs. Emerging data raised concerns of an increased risk of cardiovascular events (including heart attacks and strokes) and a risk for the occurrence of serious skin reactions for this class of medicines.

4. What are NSAIDs?

NSAIDs are non-steroidal anti-inflammatory drugs that have been available on the market for many years and are important in the treatment of arthritis and other painful conditions.
Anti-inflammatory medicines have the potential to cause stomach and gut (gastro-intestinal) side effects (e.g. ulcers and bleeding), which in rare cases can be serious or even fatal.

5. Which COX-2 inhibitors have been reviewed ?

The COX-2 inhibitors that were reviewed are celecoxib, etoricoxib, lumiracoxib, parecoxib and valdecoxib.

Lumiracoxib is currently only authorised in the United Kingdom and is not yet being marketed.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 09
E-mail: mail@emea.eu.int http://www.emea.eu.int

6. What are the risks shown by the clinical studies ?

The CHMP has reviewed detailed data from clinical trials, including long-term use as well as all available scientific evidence on this class of medicines. In its review the CHMP found an increased risk of thrombotic adverse cardiovascular events (such as heart attacks and strokes) for COX-2 inhibitors as a class.

Available data also suggest that the risk of such cardiovascular events increases with high doses and prolonged treatment with COX-2 inhibitors.
In addition, the CHMP reviewed data on rare, but serious and sometimes fatal, skin reactions, which can occur with all COX-2 inhibitors.

7. Is EMEA restricting the use of COX-2 inhibitors based on CHMP findings?

Based on the available scientific evidence the Committee for Medicinal Products for Human Use (CHMP) concluded that additional warnings and contraindications are necessary for celecoxib, etoricoxib, lumiracoxib and parecoxib. For valdecoxib the Committee concluded that the additional risks of serious and potentially fatal skin reactions associated with the use of the product outweigh its benefits and recommended the suspension of the marketing authorisation.

8. Why has Bextra (valdecoxib) been suspended and not its prodrug Dynastat (parecoxib)?

Although parecoxib is converted into valdecoxib in the body (i.e. it is a prodrug of valdecoxib), it is different from valdecoxib, as it is given by injection and is only used in very short treatment periods, often for pain relief after surgery [see European Public Assessment Reports for Bextra and Dynastat]. During the review of COX-2 inhibitors, data on parecoxib showed very rare occurrence of serious skin reaction (none of which fatal). On the basis of the overall safety data provided for parecoxib the Committee therefore considered that the benefits continue to outweigh the risks.

9. What is the new advice from EMEA and CHMP?

The CHMP has confirmed its previous findings and recommendations regarding cardiovascular safety given during the course of the review. In addition to new contraindications and warnings implemented in February 2005 a contraindication for patients with peripheral arterial disease (poor circulation to the legs or feet sometimes causing pain on walking or skin ulcers) was introduced and warnings on serious skin reactions were strengthened.

In summary the CHMP made the following recommendations:

- Prescribers and patients are advised that COX-2 inhibitors must not be used in patients with established ischaemic heart disease and/or cerebrovascular disease (stroke), and also in patients with peripheral arterial disease.
- Healthcare professionals are advised to exercise caution when prescribing COX-2 inhibitors to patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking.
- Given the association between cardiovascular risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment.
- The balance of cardiovascular and gastrointestinal risks should be carefully considered for patients who do not have heart disease but are taking low dose aspirin. Evidence suggests that any gastrointestinal safety advantage for COX-2 inhibitors is substantially reduced when given with aspirin.
- Healthcare professionals and patients are advised that hypersensitivity reactions and rare, but serious and sometimes fatal, skin reactions can occur with all COX-2 inhibitors. In the majority of cases these occur in the first month of use and prescribers are warned that patients with a history of drug allergies may be at greater risk.

10. Should patients switch from COX-2 inhibitors to conventional NSAIDs ?

The choice of treatment with COX-2 inhibitors or other analgesics/anti-inflammatory medicines is made depending on individual patient characteristics. All treatment decisions should take into account previous medical history and identified risk factors. COX-2 inhibitors should not be prescribed for those patients with ischaemic heart disease, stroke or peripheral arterial disease (poor circulation to the legs or feet sometimes causing pain on walking or skin ulcers). Patients and healthcare providers are advised to follow the latest recommendations and guidelines for the use of COX-2 inhibitors provided by the national authorities in the Member States.

11. What is the advice for patients taking COX-2 inhibitors?

- Patients treated with COX-2 inhibitors who have previously been diagnosed as having a stroke, mini-stroke, coronary heart disease or peripheral arterial disease (poor circulation to the legs or feet sometimes causing pain on walking or skin ulcers), should make a non-urgent appointment to see their doctor who will review their medication and recommend alternative treatment.
- Patients are advised that stopping COX-2 treatment will not cause any harm, but they are likely to need alternative treatment to control symptoms.
- Patients who have risk factors for heart disease or stroke (high blood pressure, high cholesterol, diabetes or those who smoke) do not need to stop treatment, but should discuss their treatment with their doctor at their next routine appointment. He/she will consider whether it would be better to continue with their COX-2 inhibitor or change to another type of treatment, depending on their overall cardiovascular (heart, blood vessel) risks and risks of suffering gastrointestinal (stomach, gut) problems.

12. Is the Europe-wide review of COX-2 inhibitors now complete?

The CHMP has now concluded its review of COX-2 inhibitors. The opinion will be sent to the European Commission in order to be transformed into a decision, which officially formalises the changes.

13. The Committee is now turning its attention to the wider class of NSAIDs. What are the safety concerns with NSAIDs?

The Committee assessed safety data for COX-2 inhibitors versus conventional NSAIDs during the course of the review procedure for the COX-2 inhibitors. On the basis of these data the Committee is now looking at the safety profile of NSAIDs, in particular cardiovascular safety, to determine the possible need for further steps.

14. What is the advice for patients taking NSAIDs?

Pending any future action, healthcare professionals and patients should closely follow the product information for conventional NSAIDs (whether prescription or non-prescription) and COX-2 inhibitors. Patients who have concerns or questions should talk to their doctor or pharmacist.