SCIENTIFIC CONCLUSIONS FOR AMENDMENT OF PRODUCT INFORMATION

In September 2004, the Marketing Authorisation Holder (MAH) of rofecoxib (a selective Cox-2-inhibitor) informed the EMEA that new clinical trial (APPROVe) data for rofecoxib have revealed a risk of thrombotic cardiovascular (CV) events. These data resulted in the worldwide withdrawal of Vioxx (rofecoxib) from the market on 30 September 2004 by the MAH and raised questions regarding the cardiovascular safety of other Cox-2 inhibitors.

Further to discussions at the CHMP October 2004 plenary meeting, the European Commission recommended that this public health issue on all aspects of cardiovascular safety including thrombotic events and cardio-renal events is the subject of Community referrals under Article 31 of Directive 2001/83/EC, as amended regarding decentrally authorised products containing celecoxib, etoricoxib and lumiracoxib and subject to a review procedure under Article 18 of Council Regulation (EEC) No 2309/93, as amended regarding the centrally authorised products containing celecoxib (Onsenal), parecoxib (Dynastat/Rayzon) and valdecoxib (Bextra/Valdyn), which were started in November 2004.

During the CHMP meeting of February 2005, discussions on cardiovascular safety took place. The CHMP agreed that an Urgent Safety Restriction (USR) on cardiovascular safety was needed to introduce new contraindications and strengthen warnings and information on side effects in the SPC and the Package Leaflet (PL). This USR was initiated on 16 February 2005 and finalised on 17 February 2005.

On 7 April 2005, the FDA (Food and Drug Administration) and the EMEA requested that Pfizer voluntarily withdraw Bextra (valdecoxib) from the market and Pfizer agreed to suspend sale and marketing of Bextra worldwide pending further discussions on the unfavorable risk versus benefit due to data on serious skin reactions.

On 20 April 2005, Pfizer presented data on serious skin reactions for valdecoxib during a hearing.

Further to a request from the European Commission, the scope of the ongoing class review was broadened to include the assessment of serious skin reactions in addition to the cardiovascular safety aspects.

Between November 2004 and June 2005, the MAH made oral explanations to the CHMP on cardiovascular and skin safety aspects for Dynastat on 18 January, 20 April and 25 May 2005.

On 23 June 2005, the CHMP concluded that:

- Further to the assessment of:
  - the new data provided on rofecoxib by the APPROVe clinical study, which revealed a risk of thrombotic CV events,
  - the data on celecoxib presented in the APC study, which suggested a dose-related increased risk of serious CV events,
  - the data on valdecoxib and parecoxib presented in the CABG (Coronary Artery Bypass Graft) and in the CABG II studies, which showed a higher rate of serious CV thromboembolic events in the parecoxib/valdecoxib treatment arm compared to the group of patients receiving placebo,
  - the data on etoricoxib in the EDGE study and pooled analyses of other clinical trials, which suggested an association with a higher thrombotic risk than naproxen,
  - the data on lumiracoxib in the Target study, which suggested a small increase in thrombotic events (especially myocardial infarction) versus naproxen,

all available data show an increased risk of CV adverse reactions for Cox-2 inhibitors as a class and agreed that there is an association between duration and dose of intake and the probability of suffering a CV reaction.

- Further to the assessment of the data on serious skin reactions, parecoxib is associated with very rare occurrence of serious skin reactions, as evidenced in post-marketing surveillance.

The CHMP confirmed changes to the Product Information already introduced through a type II variation adopted in April 2005 further to the February USR and requested further changes.

The changes of the Product Information related to the CV can be summarised as follows:

- Addition of a statement that decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks,
- Addition of the contraindications *Established ischaemic heart disease and/or cerebrovascular disease* and *Peripheral arterial disease*,
- Addition of a warning for patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking,
- Addition of a warning for prescribers to consider discontinuation of therapy if during treatment, patients deteriorate in any of the organ system functions described,
- Addition of a warning for prescribers not to discontinue antiplatelet therapies,

The changes of the Product Information related to the SCAR can be summarised as follows:

- Addition of a contra-indication for *patients with a history of any drug allergy*,
- Addition of a warning to report that the onset of skin reactions occur in the majority of cases within the first month of treatment,
- Addition of a warning for prescribers to monitor any serious skin reactions, which could occur during the treatment,
- Addition of a warning for patients to immediately report any emergent skin condition to their physician.

GROUNDS FOR AMENDMENT OF PRODUCT INFORMATION

Whereas, the CHMP

- is of the Opinion that the benefit/risk balance of Dynastat in the short-term treatment of postoperative pain remains favourable and the Marketing Authorisations should be maintained according to revised Summaries of Product Characteristics and Package Leaflet (attached in Annex I and IIIB, respectively of the CHMP Opinion),
- concluded that the cardiovascular safety and serious skin reactions should be continuously and carefully monitored and assessed,
- recommended follow-up measures to further investigate the safety of parecoxib.