NOTIFICATION OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
FAX NUMBER –44 20 75237051

This notification is an official referral under Article 31 of Directive 2001/83/EU made by the United Kingdom

Product Name(s), if appropriate,	Diclofenac containing medicinal products
Active Substance	Systemic formulations of diclofenac (eg oral, IM, and IV)
Marketing Authorisation Holder(s)	Various

Diclofenac is a non-selective Non-Steroidal Anti-Inflammatory Drug (NSAID) which is authorised for the relief of pain and inflammation in a wide range of conditions including arthritic conditions and acute musculoskeletal disorders. It is currently available in the EU in a number of different formulations.

In 2006, the risk of thrombotic events associated with NSAIDs was reviewed by the CHMP. This followed on from previous reviews on the cardiovascular safety of selective Cyclooxygenase-2 (COX-2) inhibitors (coxibs). These reviews concluded that:

- coxibs as a class, may cause an increased risk of thrombotic events compared with placebo and some non-selective NSAIDs, and that this effect may be dose-dependent and duration-dependent
- a small increase in the absolute risk for thrombotic events especially when used at high doses for long-term treatment could not be excluded for non-selective NSAIDs

The available evidence at the time, suggested that between non-selective NSAIDs, diclofenac was probably associated with the highest risk for thrombotic events. Warnings about the risk of thrombotic events were added to the product information for all NSAIDs, including diclofenac, and communicated throughout Europe. However, the data were not considered sufficient to conclude that the magnitude of this increased risk was in the same range as that for coxibs.

Since 2006, a number of additional studies further investigating the relative cardiovascular safety of these drugs have been published. These studies along with data from the European Commission funded SOS study have been the subject of a recent review by the CHMP following a request from the UK for a scientific opinion under Article 5(3) of Regulation (EC) 726/2004. This review concluded at the October CHMP plenary meeting that despite significant differences between these studies in

their methodological approaches, the accumulating evidence shows remarkable consistency in the reported results for diclofenac, which appears to be associated with thrombotic risks similar to those of coxibs. No information on topical diclofenac containing products was available for this review, however, due to their low systemic exposure it is unlikely that they are associated with significant risks.

In considering the potential urgency of this issue we have taken into account the fact the majority of these new studies are already in the public domain and whilst they provide clarification on the magnitude of the risk they have not identified a new safety concern with diclofenac. The product information for diclofenac already includes warnings in respect of the identified risks of thrombotic events for healthcare professionals and patients but the UK considers that there may be a need for further revisions in order to bring it in line with the evidence currently available.

In light of the above, and given the widespread use of diclofenac, the UK considers that it is in the interest of the Union to refer diclofenac containing products for systemic use (i.e. excluding topical formulations) to the Pharmacovigilance Risk Assessment Committee and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC, as amended, on the whether risk of thrombotic events impacts on the balance of benefits and risks and also whether the marketing authorisations for medicinal products containing diclofenac should be maintained, varied, suspended or withdrawn.

A draft list of questions to be submitted to the MAH is annexed.

Signed

Professor Sir Kent Woods
Chief Executive

Date

17 October 2012

ANNEX A

List of questions for MAHs for products containing diclofenac.

The MAHs for diclofenac are asked to provide answers to the following questions:

Question No. 1
How is diclofenac used?
Please provide:

- Information on the currently authorised diclofenac containing products in the different Member States and their current marketing status including information on approved indications(s), doses, treatment duration, contraindications, warnings and precautions included in the summary of product characteristics

- Information on sales figures and estimated patient exposure for diclofenac. This should include a yearly breakdown of sales and exposure over the last 10 years for each Member State

Question No. 2
What is the evidence for the risk of thrombotic events associated with diclofenac?
Please provide a detailed analysis of the thrombotic risks associated with diclofenac from:

- Clinical trials;
- Pharmacoepidemiological studies;
- Published literature

In reviewing this data, please include a meta-analysis of:

1. randomised clinical trials
2. observational studies

which included patients treated with diclofenac (compared to placebo, other NSAIDs or COX-2 inhibitors) for events of stroke, myocardial infarction and other relevant cardiovascular endpoints.

Please also provide a comprehensive comparison of the thrombotic risks associated with diclofenac with those of other non-selective NSAIDs and COX-2 inhibitors, and provide an estimate of the absolute risk (i.e. Additional serious cardiovascular events per 1000 patient years exposure, relative to no treatment or selective COX-2 inhibitor). As far as possible, please comment on the level of risk at different licensed doses of diclofenac.

Question No.3
What is your analysis of the balance of risks and benefits of diclofenac?
A benefit/risk assessment of diclofenac in its licensed indication(s), and whether this is modified by the thrombotic risk in any indications or populations. This should include proposals and justification with supportive evidence for any measures including changes to the SPC/PIL which may improve the benefit/risk of diclofenac and how their impact should be monitored.