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/EC made by United Kingdom:

Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s): Active Substance(s)	Ibuprofen containing medicinal products - Systemic formulations (oral formulations, transdermal patches, rectal preparations). Excludes products authorised for use solely in children and topical preparations intended for local effects with low systemic absorption (e.g. creams, gels, sprays, vaginal and ophthalmic preparations) Ibuprofen, dexibuprofen
Marketing Authorisation Holder(s)	Various

Ibuprofen is a non-selective Non-Steroidal Anti-Inflammatory Drug (NSAID) which is authorised for relief of pain and inflammation in a wide range of conditions including arthritic conditions and 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 Committee on Medicinal Products for Human Use (CHMP). This review 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 and for long-term treatment could not be excluded for non-selective NSAIDs

Since 2006, a number of additional studies have been published that have further examined the relative cardiovascular safety of NSAIDs, e.g. several meta-analyses of clinical trials and of observational studies. These studies, along with data from the EU Commission funded SOS study, were subject of a review by the CHMP in 2011/2012, following a request from the UK for a scientific opinion under Art. 5(3) of Regulation (EC) 726/2004. This review concluded at the October 2012 CHMP meeting that, concerning ibuprofen, the available data was inconsistent with regard to the relative cardiovascular risk, as compared to coxibs.

Further new data on cardiovascular and gastrointestinal effects of NSAIDs became available recently. The Coxib and traditional NSAID Trialists' (CNT) collaborative group published results from a large meta-analysis of more than 600 randomised clinical trials[1]. The results suggest that the cardiovascular risk with high dose diclofenac is similar to selective COX-2 inhibitors, but also indicate that the risk with high-dose ibuprofen (2400mg) may also be similar to COX-2 inhibitors. In addition, there is accumulating evidence[2],[3] that ibuprofen may also inhibit the antiplatelet action of low-dose aspirin for cardiovascular prophylaxis.

In considering the potential urgency of this issue we have taken into consideration the fact that this does not relate to a new safety issue for ibuprofen. The ibuprofen product information for healthcare professionals and patients already includes information about the increased risk of thrombotic events with long-term use of high doses. But there is a need to consider the impact of evidence newly available since the previous Europe-wide review of all NSAIDs on the adequacy of the contraindications, precautions and warnings for ibuprofen containing medicinal products, and whether the advice on interaction with aspirin is sufficient to minimize the risk of failure of its cardiovascular prophylactic action.

In light of the above, and given the widespread use of ibuprofen, UK considers that it is in the interest of the Union to refer ibuprofen containing products for systemic use to the PRAC and requests, that it gives its recommendation under Article 31 of Directive 2001/83/EC as amended, on whether the new evidence on the risk of thrombotic events when used at high doses, doses at or above 2400mg per day in adults and new evidence on interaction with low-dose aspirin require any updates to the advice to healthcare professionals and patients including warnings or contraindications as expressed in the current ibuprofen product information, or whether any other regulatory measure would be needed.

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[1] Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Coxib and traditional NSAID Trialists' (CNT) Collaboration. The Lancet - 30 May 2013

[2] Hohlfeld T (2013); Thrombosis and Haemostasis; 109: 825–833

[3] MacDonald TM, Wei L. Lancet 2003;361:573-4

Signed [redacted] Date9th June 2014