European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 7 November 2006
EMEA/CHMP/442130/2006

PUBLIC CHMP ASSESSMENT REPORT

FOR

MEDICINAL PRODUCTS CONTAINING NON-SELECTIVE NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Procedure No. EMEA/H/A-5.3/800

under Article 5(3) of Regulation (EC) No 726/2004

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1 SCIENTIFIC DISCUSSION

1.1 Introduction

NSAIDs including Cox-2 inhibitors are widely used among patients of all ages. They are available on prescription but some NSAIDs have also been approved for over the counter (OTC use) for short-term treatment. The products are effective for symptomatic relief of mild to moderate painful conditions, such as headache and trauma. Long-term use of the higher doses is mainly indicated for relief of pain of musculoskeletal origin, with or without inflammatory background disease. NSAIDs do not provide curative treatment, but the value of the symptomatic relief in many patients is undisputed.

The adverse event profile of NSAIDs, including Cox-2 inhibitors, is recognised. Gastrointestinal adverse events, including serious events of PUB (perforation, ulcer, bleeding) are one main reason for discontinuation of treatment with NSAIDs. Other events such as hypersensitivity or skin reactions, cardiorenal effects and hepatotoxicity are class effects, although the exact incidence may vary between products. These events are well known, and have been addressed in depth in the previous Cox-2 referrals and Pharmacovigilance Working Party (PhVWP) review of non-selective NSAIDs. These reviews also resulted in improved labelling to address these risks.

New information from clinical trials and epidemiological studies has recently emerged in relation to the cardiovascular safety of Cox-2 inhibitors and non-selective NSAIDs.

1.2 CHMP conclusions from previous assessments

1.2.1 Cox-2 review procedure

In June 2005, the CHMP adopted an opinion for the Cox-2 review procedure[1]. The CHMP concluded that an increased risk of cardiovascular adverse reactions for Cox-2 inhibitors is regarded as a class effect. There is an association between duration and dose of intake and the probability of suffering a cardiovascular reaction.

The CHMP considered that, further to the assessment of the data provided by the MAHs, the benefit/risk balance of medicinal products containing Cox-2 inhibitors in the agreed indications is favourable and the Marketing Authorisations should be maintained according to revised Summaries of Product Characteristics.

In April 2005, the US 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 unfavourable risk/benefit balance due to data on serious skin reactions. The European marketing authorisation for Bextra is currently suspended.

1.2.2 CHMP conclusions and recommendations on non-selective NSAIDs published in October 2005

During its October 2005 meeting, the CHMP discussed the outcome of the extensive assessments made within the PhVWP, of the available data in relation to cardiovascular and gastrointestinal safety, and severe cutaneous adverse reactions for diclofenac, etodolac, ibuprofen, indomethacin, ketoprofen, meloxicam, nabumetone, naproxen, nimesulide and piroxicam. It was concluded that: *No new safety concern has been identified that would warrant a formal Article 31 (*Directive 2001/83/EC, as amended) *referral to the CHMP*. However, it was decided to perform a full assessment of benefit/risk

[1] Press release – European Medicines Agency concludes action on COX-2 inhibitors – London, 27 June 2005 – Doc. Ref. EMEA/207766/2005

balance for piroxicam, ketoprofen and ketorolac. This assessment was finalised in September 2006 (see below).

However, it was noted that there was a disharmony in relation to already well-known cardiovascular, gastrointestinal and skin safety information in NSAID SPCs across the European Union (EU). Consequently key elements to amend sections 4.3 *Contra-indications*, 4.4 *Special Warnings and Precautions for Use*, 4.5 *Interactions with other medicines and other forms of interaction* and 4.8 *Undesirable effects* of the SPC of non-selective NSAIDs were discussed and adopted. It was also concluded that these key elements should be implemented at national level. Communication material[2] was published to inform patients and prescribers of this review.

1.2.3 CHMP conclusion and recommendation published in September 2006 for piroxicam, ketoprofen and ketorolac

In the review finalised at the October 2005 meeting, the need for further evaluation of the benefits and risks of piroxicam, ketoprofen and ketorolac was identified.

Subsequent review resulted in stronger warnings for cardiovascular safety, gastro-intestinal safety and skin reactions for all three compounds, to promote more cautious use. The product information should be amended with agreed additional key elements. It was also concluded that:

- The benefits of **ketoprofen** outweigh its risks for daily doses up to a maximum of 200 mg.
- The benefits of **ketorolac** outweigh its risks in its approved short-term use.
- **Piroxicam** may have a less favourable gastrointestional safety profile and a higher risk of skin reactions than that of other non-selective NSAIDs and a formal assessment procedure should be started.

A formal Article 31 referral for piroxicam has been initiated in September 2006, and is ongoing.

1.3 New data since previous CHMP conclusions

Since the assessments reflected above, new data sets have become available. The most important sources are:

- **MEDAL[3] programme (etoricoxib and diclofenac):** Preliminary data
- **APC[4] and PreSAP[5] - celecoxib:** Final study reports
- **Epidemiology – naproxen, diclofenac and ibuprofen, meloxicam:**
  - Updated meta-analyses of published epidemiological studies
  - Meta-analysis by McGettigan et al. (2006)
  - Meta-analysis by Hernandez-Diaz S et al. (2006)
  - MAH sponsored data from three studies on meloxicam and the risk of myocardial infarction (GPRD[6], Veteran's administration, RAMQ databases)

[2] Press release - EMEA update on non-selective NSAIDs - London, 17 October 2005 - Doc. Ref. EMEA/298964/2005
[3] Multinational Etoricoxib versus Diclofenac Arthritis Long-term
[4] Adenoma Prevention with Celecoxib
[5] Prevention of Colorectal Sporadic Adenomatous Polyps
[6] General Practice Research Database

1.4 Summary and assessment of current data

1.4.1 Pharmacodynamic properties

Pharmacodynamic properties related to cardiovascular safety for non-selective NSAIDs, also addressing Cox-2 selectivity, were discussed in depth in the PhVWP review undertaken last year.

The conclusions of this review were as follows:

In vitro studies have shown some NSAIDs to be Cox-2 selective, having little or no effect on Cox-1 at therapeutic doses (all Cox-2 inhibitors), others to be less Cox-2 selective, having some effect on Cox-1 at therapeutic doses (nimesulide, meloxicam, etodolac, nabumetone, diclofenac) and others to be non-selective or preferentially Cox-1 selective (ketoprofen, naproxen, ibuprofen, indomethacin, piroxicam). However results from *in vitro* studies vary due to differences in technique and should only serve as a guide to Cox selectivity *in vivo*.

The clinical relevance of Cox selectivity *in vitro* with regards to cardiovascular risk is unclear. One of the possible mechanisms for the cardiovascular risk seen with the Cox-2 inhibitors is an unfavourable prostacylin (PGI2)/thromboxane (TXA2) ratio resulting from the selective inhibition of PGI2. Selective Cox-2 inhibitors have no effect on platelet function at therapeutic doses. However it has been shown that TXA2 formation must be inhibited by at least 95% to have a clinical effect on platelet function. Therefore drugs such as etodolac and meloxicam, despite being able to inhibit Cox-1 to some degree at therapeutic doses have negligible effects on platelet function, but it is not clear whether they share other cardiovascular effects of the more specific Cox-2 inhibitors class (e.g. possible effects on atheromatous plaques, ischaemic preconditioning).

Indirect renal effects have also been proposed as a possible mechanism for increased cardiovascular risk. In this respect it has been shown that Cox-2 selective drugs offer no protection to the kidney and cause similar cardiorenal adverse effects seen with non-selective NSAIDs, although there is some variability between products.

Aspirin irreversibly binds to Cox-1 and is able to offer cardiovascular protection by inhibition of platelet function. Many patients on aspirin also require conventional NSAIDs as analgesia for arthritic conditions. The question of NSAIDs being able to interfere with the inhibition of Cox-1 by aspirin has been raised by mechanistic studies. The more selective a drug is for Cox-2, the less likely it is to interact with aspirin. Ibuprofen has been shown to interact with aspirin *ex vivo*, reducing its inhibition of Cox-1. However, observational studies and clinical trials have shown inconclusive results regarding the effect of combination of NSAIDs and aspirin therapy on mortality risk and incidence of myocardial infarction, and no firm conclusions are possible.

Naproxen during continuous treatment at clinically relevant doses inhibits platelet Cox-1 to an extent that might be sufficient for cardiovascular and cerebrovascular protection, although this has not been established in clinical studies. However, it is not known whether the inhibiting effect on Cox-2 might adversely influence the potentially advantageous antiplatelet effect of naproxen. It cannot be conclusively determined whether treatment with naproxen (particularly at irregular dosing and/or low doses) in addition to aspirin could reduce the antithrombotic effect of aspirin.

Discussion:

The conclusions drawn in 2005 remain valid. It should be pointed out that there is a lack of knowledge as to whether and how *in vitro* or *ex vivo* results for Cox-1/Cox-2-inhibition of the different NSAIDs correlate to effects in the vascular system. Thus, it is uncertain to extrapolate *in vitro*/*ex vivo* data to potential effects after (long-term) Cox-inhibition *in vivo*. Furthermore, the cardiorenal effects of NSAIDs, being a dose-related class effect, may also be an important contributor to long-term thrombotic cardiovascular risk. As pointed out above, Cox-2 selectivity does not appear to have an impact on degree of cardiorenal effects.

1.4.2 Gastrointestinal Safety

Non-selective NSAIDs

During the PhVWP review, which was finalised in October 2005, the gastrointestinal safety of the non-selective NSAIDs was assessed in depth. Thereafter, some additional data have emerged, e.g. new epidemiology data, as well as information from the MEDAL programme.

Discussion on gastrointestinal safety

All NSAIDs are associated with gastrointestinal toxicity, but the available data do not allow for precise quantification of the risk of serious gastrointestinal reactions with different NSAIDs, nor on the time or dose-dependency of such risks. The available evidence from epidemiological studies and from spontaneous adverse drug reaction (ADR) reports suggests that upper gastrointestinal toxicity with NSAIDs may vary between products. To some extent, the inter-product variation in toxicity seen in epidemiological studies is likely to be influenced by usage patterns. For example, drugs that are used more commonly in severe inflammatory arthritis may be associated with higher rates of gastrointestinal toxicity due to co-medication with steroids, or other patient-related factors. Likewise, those drugs commonly used at the maximum recommended doses (e.g. diclofenac, naproxen) are more likely to be associated with toxicity than those routinely used at low doses (e.g. ibuprofen). Caution must also be observed in relation to comparative spontaneous ADR reports because the known limitations of this data source, including under-reporting, reporting biases, and channeling of high risk patients towards certain drugs.

Recognising the limitations of the available data, piroxicam and ketoprofen have been associated with higher relative risks, odds ratios, reporting rates and proportional reporting suggest that these products may be associated with the highest risk. The consistency across different analyses is particularly striking for piroxicam. Doses of piroxicam (more than) >20 mg and doses of ketoprofen (more and equal) ≥ 200 mg may represent particularly high risks.

It is not possible to reach firm conclusions on the relative gastrointestinal toxicity of the other products. However, it seems that naproxen and indometacin may be associated with a slightly higher risk than diclofenac and particularly ibuprofen, although evidence for drawing such conclusions is weak. For ibuprofen, the use of low doses for short-term conditions may have biased the results relative to some other products.

Risk factors

The majority of studies with sufficient data have demonstrated a strong association between increasing dose and increasing risk of gastrointestinal toxicity. Another strong risk factor is the concomitant use of more than one NSAID or aspirin. After adjustment for confounding factors no statistically significant differences in the risk according to indication have been found. Other risk factors identified, namely increasing age, a history of peptic ulcer disease, male gender, the use of oral anticoagulants or oral corticosteroids, treatments for heart disease and diabetes or being a smoker/heavy drinker, are generally well recognised. There is some controversy over the effect of duration of use, with some studies identifying the highest risk in early use. The risk decreases rapidly upon stopping NSAID treatment.

The newly available data do not alter these conclusions. The key elements agreed by the CHMP and published in October 2005 for (all non-selective NSAIDs) and September 2006 (specific wording for piroxicam, ketolorac and ketoprofen) are considered adequate to address gastrointestinal safety.

Cox-2 inhibitors

One main reason for the development of the Cox-2 inhibitors, was a hypothesis that by diminishing Cox-1 inhibition, the gastrointestinal safety would be improved, while the therapeutic effects (anti-inflammatory and analgesic) would remain, via a selective Cox-2 inhibition. However, the gastrointestinal benefit of Cox-2 inhibitors vs. non-selective NSAIDs has been debated. There is evidence of improved gastrointestinal safety for Cox-2 inhibitors relative to NSAIDs, e.g. from data indicating a better overall tolerability for Cox-2 inhibitors. However, data from e.g. the CLASS trial (celecoxib vs. ibuprofen or diclofenac) and the MEDAL programme (etoricoxib vs. diclofenac) show no significant benefit of the Cox-2 inhibitors for "complicated" gastrointestinal events, particularly in patients taking aspirin/anti-platelet agents. Although most evidence suggests a gastrointestinal benefit for Cox-2 inhibitors, further data are needed.

1.4.3 Cardiovascular safety

The cardiovascular safety of Cox-2 inhibitors has been discussed within two CHMP review procedures. The first one was initiated in July 2002, due to the finding of a possible increased risk of arterial thrombotic events for rofecoxib in the VIGOR study, as well as arterial thrombotic events reported post-marketing for celecoxib and rofecoxib. The second review procedure was initiated in October 2004, following the withdrawal of rofecoxib from the market due to data of an increased risk of serious thrombotic events with rofecoxib in the placebo controlled APPROVe study. Subsequently, the PhVWP has reviewed the cardiovascular safety for non-selective NSAIDs in depth, and CHMP conclusions have been drawn as reflected above. This review included both cardiorenal and thrombotic effects.

The PhVWP concluded that 'Cardiorenal effects of NSAIDs are a class effect and are dose-related. Such effects may be an important contributor to long-term cardiovascular risk. The available data do not suggest that differences in cardiorenal effects between products are related to Cox-2 selectivity. The review (finalised in October 2005) resulted in agreed key elements for the SPC, as it had been noted that there were inconsistencies between substances and Member States, for contraindications and warnings related to cardiorenal effects (hypertension, heart failure, oedema).

The main focus of recent discussions has been on thrombotic cardiovascular risk. When trying to assess the thrombotic risk profile for Cox-2 inhibitors and non-selective NSAIDs, in available clinical trials, there are a number of limitations which make such assessment difficult. Firstly, only few trials are of sufficient size and duration to provide useful data. Further, the fact that all trials except ADAPT, compare either Cox-2 inhibitor vs. placebo, or Cox-2 inhibitor vs. non-selective NSAID, precludes a complete cross – class comparison. In addition, the endpoints reported across trials are not always equivalent, making comparisons difficult. Other complicating factors are that supratherapeutic doses have been used in several trials, particularly for the Cox-2 inhibitors, or that in some trials the maximum dose for one compound has been used while a dose below the maximum was used for the comparator.

Despite the large amount of data available, a number of uncertainties remain. These include further comparative data for cardiovascular and gastrointestinal effects (risks and benefits) as well as other undesirable effects between Cox-2 inhibitors and non-selective NSAIDs, at therapeutic doses, and in patients with different levels of risk factors, and in different disease conditions. In addition, placebo comparisons for non-selective NSAIDs and some Cox-2 inhibitors addressing the same areas are currently unavailable. Further, the impact of concomitant use of Cox-2 inhibitors / NSAID and acetylsalicylic acid (ASA) is still not clear. Some of these questions may be addressed in ongoing and/or planned studies.

Below is a summary of the clinical trials with Cox-2 inhibitors and NSAIDs, which contribute data for this topic.

1.4.3.1 Summary of clinical trials of importance for thrombotic cardiovascular safety.

- APPROVe

The APPROVe (Adenomatous Polyp Prevention On Vioxx) study (Protocol 122) was a randomised, double-blind placebo-controlled study that compared the effect of rofecoxib 25 mg to placebo on the recurrence of neoplastic polyps in patients with a history of colorectal adenomas over 3 years. Approximately 2,500 patients were enrolled into the study and about 550 patients had completed the study when it was terminated in September 2004, when Vioxx was withdrawn from the market.

- VIGOR

The VIGOR study aimed to examine the gastrointestinal safety of rofecoxib 50 mg once daily (twice the maximum recommended dose for chronic use) versus naproxen 500 mg twice daily, in patients with rheumatoid arthritis. Patients were not permitted to take low-dose acetylsalicylic acid for cardiovascular protection. Approximately 8,000 patients were included, and the median study duration was 9 months.

- VICTOR

The VICTOR study (VIOXX in Colorectal Cancer Therapy; definition of Optimal Regime) was a randomised, double-blind, placebo-controlled study of rofecoxib in colorectal cancer patients following potentially curative therapy to determine the effect of rofecoxib on colorectal reccurrence. Approximately 2,400 patients were enrolled, of which about 1,100 patients received study drug for more than or equal to 1 year, and about 250 patients for more than or equal to 2 years. The study was prematurely terminated.

- CLASS

In the Celecoxib Long-Term Arthritis Safety Study (CLASS) 8,059 patients with osteoarthritis (OA) or rheumatoid arthritis (RA) were randomised (7,968 patients were treated) to receive celecoxib 400 mg twice daily (BID) (2-4 times the labeled dose for OA, twice the labeled dose for RA), diclofenac 75 mg BID, or ibuprofen 800 mg three times daily (TID) for up to 15 months (median duration 6 to 9 months). Patient characteristics, including ASA use (21% to 22% of patients), history of cardiovascular disease (40% of patients in all treatment groups), and cardiovascular risk factors, were balanced across treatment groups. The primary objective of the study was to compare the incidence of clinically significant upper gastrointestinal events across treatment groups. Results of the study showed lower incidence of such events for the celecoxib 400 mg BID treatment group compared to the non-selective NSAID treatment groups combined. However, diclofenac seemed to have a better gastrointestinal safety profile than ibuprofen, and no significant differences in gastrointestinal risks between celecoxib and diclofenac were shown. In addition, the advantage of celecoxib over NSAIDs was no longer significant with concomitant ASA use.

The cardiovascular safety results of the CLASS trial showed no significant increase in the percentage of patients with serious cardiovascular thromboembolic adverse events for celecoxib (1.3% of patients) versus diclofenac (1.4% of patients) or ibuprofen (1.1% of patients). Table 1 lists individual serious cardiovascular thromboembolic adverse events. Not unexpectedly, percentages of patients with serious cardiovascular thromboembolic adverse events were higher in patients who used low-dose ASA compared with non-ASA users (see discussion for ibuprofen interaction with ASA below).

Table 1. Serious Cardiovascular Thromboembolic Adverse Events: CLASS (Number of Patients [Events per 100 Patient-Years])

Adverse Event Category Adverse Event	Celecoxib 400 mg BID N = 3,987	Diclofenac 75 mg BID N = 1,996	Ibuprofen 800 mg TID N = 1,985
Myocardial Events			
Cardiac arrest	1 (<0.1)	4 (0.4)	1 (<0.1)
Myocardial infarction	19 (0.8)	4 (0.4)	9 (0.8)
Myocardial ischemia	1 (<0.1)	2 (0.2)	0 (0.0)
Tachycardia ventricular	3 (0.1)	1 (<0.1)	0 (0.0)
Unstable angina	8 (0.3)	4 (0.4)	0 (0.0)
Cerebrovascular Events			
Cerebrovascular disorder	4 (0.2)	6 (0.6)	6 (0.5)
Peripheral Vascular Events			
Embolism	1 (<0.1)	0 (0.0)	0 (0.0)
Embolism pulmonary	4 (0.2)	1 (<0.1)	2 (0.2)
Peripheral vascular disease	0 (0.0)	0 (0.0)	1 (<0.1)
Thrombophlebitis deep	7 (0.3)	5 (0.5)	1 (<0.1)
Thrombophlebitis leg deep	1 (<0.1)	1 (<0.1)	0 (0.0)

N = Number of patients; BID = Twice daily; TID = Three times daily.
Source: Study Report for Study N49-98-02-035/102, Table T43.

- APC / PreSAP

The APC (prevention of sporadic colorectal adenomas with celecoxib) trial and the PreSAP (Prevention of colorectal sporadic adenomatous polyps) trial were double-blind, randomised studies in which subjects who had undergone colonoscopic resection of all evident colorectal adenomas were stratified according to use of low-dose ASA and treated with celecoxib or placebo for 3 years.

In the APC trial, subjects were randomised in a 1:1:1 ratio to placebo, celecoxib 200 mg BID, or celecoxib 400 mg BID. In the PreSAP trial, subjects were randomised in a 2:3 ratio to either placebo or celecoxib 400 mg once daily (QD). The 400 mg total daily dose is the maximum approved celecoxib dose for treatment of RA, and is 1 to 2 times the maximum approved celecoxib dose for treatment of OA. The 400 mg BID dose is the approved dose for celecoxib in the treatment of familial adenomatous polyposis (FAP).

Study medication was suspended for all subjects in APC and PreSAP trials following notification by the respective Data Safety Monitoring Boards on 16 December 2004 that the potential for cardiovascular risk with celecoxib had been observed in the APC trial. After the suspension of study medication in December 2004, the blinded treatment extensions were amended to collect follow-up safety data for all subjects (serious adverse events only, collected at Year 1 and Year 2 after the last dose of study medication) and to offer all subjects a final colonoscopy at Year 5. These 2-year extensions remain ongoing for the purpose of follow up observation in subjects no longer being treated with study medication, and the expected last subject's last clinic visit is scheduled to occur in April 2007.

The conclusion from March 2006 remains, namely that the final cardiovascular data from APC confirm the previous signal from this trial, and that the final cardiovascular results from PreSAP showed a somewhat different pattern compared to the previous PreSAP results, now pointing towards an increased risk.

The APC study (placebo, celecoxib 200 mg BID or 400 mg BID) has shown a dose-related significant increase in cardiovascular thromboembolic risk for celecoxib compared with placebo. The relative risk for the composite endpoint of cardiovascular death, myocardial infarction, stroke, or heart failure was 2.6 (95% CI 1.1-6.1) for 200 mg BID and 3.4 (95% CI 1.5-7.9). The absolute magnitude of risk was greater for patients with a history of cardiovascular events at baseline than for patients without such history, although the relative risk is the same. In patients with a history of myocardial infarction, stroke, congestive heart failure, or angina at baseline the incidence of serious cardiovascular events was 3% for placebo and 8.8% for celecoxib at either dose (RR = 3.0, 95% CI 0.9-10.4). Among

patients without these risk factors at baseline, the corresponding figures were 0.7% for placebo and 2.1% for celecoxib (RR = 3.0, 95% CI 1.0-8.7) (Bertagnolli et al., 2006).

The PreSAP study (placebo or celecoxib 400 mg once daily) showed a smaller increase in cardiovascular events compared with APC study. The relative risk for the composite endpoint of cardiovascular death, myocardial infarction, stroke, or heart failure was 1.3 (95% CI 0.65-2.62).

When APC and PreSAP findings were integrated, the relative risk for the composite endpoint of cardiovascular death, myocardial infarction, stroke, or heart failure was 1.9 (95% CI 1.1-3.1).

Review of the final study reports of the two studies shows that there are a number of differences between the two trials in terms of dose regimens, base line characteristics, effect on blood pressures and magnitude and timing of the increased cardiovascular risk. Regarding time-to-event for the composite endpoint of cardiovascular death, myocardial infarction, stroke, or heart failure, an increased risk became apparent earlier in APC (after 8 months) than in PreSAP (after 18 months), even though an earlier harmful effect of celecoxib cannot be ruled out due to the statistical limitations of these studies. Further, the magnitude of risk with 400 mg daily dose appears higher in the APC trial than in PreSAP.

Several possible explanations for the differing results in APC and PreSAP may be discussed:
Firstly, the difference in dosing regimes - twice (APC) or once (PreSAP) daily, the role of which in the effect on blood pressure has been discussed (Solomon et al., 2006). The APC trial showed a statistically significant increase in mean systolic blood pressure compared with placebo at 1 year and 3 year follow up in both the 200 mg BID and the 400 mg BID groups, suggesting that changes in vascular tone may predispose patients to cardiovascular events. However, there was no difference in blood pressure between placebo and celecoxib 400 mg once daily in PreSAP at either 1 or 3 years. It should be noted, that the blood pressure data were from routine monitoring, and not collected with rigor appropriate for use of a prospectively defined endpoint. These results should thus be interpreted with caution.

Secondly, there are several differences in the baseline characteristics of the patients in the studies (see further below). For instance, the percentages of patients with high BMI (Body Mass Index)/obesity, hyperlipidemia, hypertension, ASA users, history of smoking, or any cardiovascular thromboembolic risk factor were higher in APC than in PreSAP.

Thirdly, the proportion of subjects exposed/followed up at a later phase (37 months) in PreSAP was lower than in APC. This might be associated with a smaller increase in a cardiovascular risk in PreSAP since the cardiovascular risk may increase with longer treatment duration.

These differences between the two studies may provide some explanation for the differences in the magnitude and/or timing of the cardiovascular risks observed. However, it could also be a chance finding, as e.g. confidence intervals for the composite cardiovascular endpoint in both studies are overlapping.

Conclusions:

The conclusions drawn by the CHMP and the recommendations given at the end of the review procedure on the Cox-2 inhibitors remain valid.

- ADAPT

The ADAPT study, a multicentre, double-blind, placebo-controlled trial of naproxen 220 mg BID or celecoxib 200 mg BID versus placebo to test whether long-term use of a non-selective NSAID (naproxen) or selective Cox-2 inhibitor (celecoxib) would reduce the incidence of Alzheimer's Disease (AD) in dementia-free, elderly subjects at risk for AD, was terminated prematurely. Only preliminary data are available.

In the most recent update from March 2005, analyses based on 2,463 participants who contributed 3,888 person-years of follow-up, up to 1 October 2004 were provided. Table 2 shows an overview of the major outcome.

Table 2. Major events (as of 1 Oct 2004)

	Cel	Nap	Pbo				
Number randomised	**704**	**702**	**1,057**				
	%Participants			**Cel vs. Pbo**		**Nap vs Pbo**	
	Cel	**Nap**	**Pbo**	**RR***	**P+**	**RR***	**P+**
Death (n-23)	0.85	1.14	0.85	1.00	1.00	1.34	0.62
Fatal or nonfatal MII (n=29)	1.42	1.28	0.95	1.49	0.37	1.34	0.49
Fatal or nonfatal stroke (n-29)	1.42	1.71	0.85	1.67	0.35	2.01	0.49
Any MI/stroke/death (n=73)	2.84	3.70	2.55	1.11	0.76	1.45	0.20
Any MI/stroke/cardiac death (n=58)	2.41	2.99	1.89	1.28	0.50	1.58	0.15
Gastrointestinal bleed (n=58)	1.56	1.99	1.14	1.37	0.52	1.75	0.16

RR - Relative Risk
P+ - values detained from Fisher's exact tests of treatment differences
MI - myocardial infarction

The data as presented, do not give firm evidence for an adverse effect of naproxen 220 mg BID, as initially suggested, or for celecoxib 200 mg BID, on serious cardiovascular outcomes. However, the risk estimates for fatal and non-fatal MI and for the composite cardiovascular endpoint are numerically greater, although not statistically significant, than unity for both products. These data lend tentative support to the results in the APC trial showing an adverse effect for celecoxib. Some differences as compared with the APC trial, should be recognised: the average duration of follow-up was shorter; the sample size was smaller; and the target population was different.

In conclusion, the preliminary ADAPT trial data show a consistent numerical trend of an adverse effect for both celecoxib and naproxen on the risk for serious cardiovascular events. However, the evidence is not conclusive since none of the risk estimates in relation to placebo was statistically significant. The results in a final publication are awaited. It is also interesting to note that gastrointestinal events were somewhat increased in the celecoxib group vs. placebo.

- MEDAL PROGRAMME

The MEDAL programme consists of three studies, EDGE, EDGE II and MEDAL, in which etocoxib is compared with diclofenac. It was designed to provide evidence of non-inferiority in relation to thrombotic events rates after daily treatment with etoricoxib (60 mg and 90 mg combined) compared with diclofenac 150 mg. The three studies were conducted in 38 countries. Table 3 shows an overview of the studies:

Table 3: Summary of studies in the MEDAL programme

	EDGE	EDGE II	MEDAL
Protocol	**061-01**	**072-02**	**066-03**
Primary Objective	Compare GI tolerability of etoricoxib to diclofenac in OA patients	Compare GI tolerability of etoricoxib to diclofenac in RA patients	Compare cardiovascular safety etoricoxib vs. diclofenac, based on data across MEDAL, EDGE II, EDGE.
Study therapy	Etoricoxib 90 mg q.d. vs. diclofenac 50 mg t.i.d. (1:1)	Etoricoxib 90 mg q.d. vs. diclofenac 75 mg b.i.d. (1:1)	Etoricoxib (60 or 90 mg in OA, 90 mg in RA) vs. diclofenac 75 mg b.i.d. (1:1)†
Study size & Indication	7,111 OA	4,086 RA	23,504 about 76% OA about 24% RA
FPI – LPO	Jun 2002 - Nov 2003	Feb 2003 - Dec 2005	Sept 2002 - May 2006

†In the MEDAL Study, the first about 4,300 osteoarthritis patients were randomised to etoricoxib 90 mg or diclofenac 75 mg b.i.d. The remaining osteoarthritis patients were randomised to etoricoxib 60 mg or diclofenac 75 mg b.i.d.
OA: Osteoarthritis; RA: Rheumatoid arthritis; GI: Gastrointestinal

Preliminary data from the MEDAL programme suggest many similarities in the overall safety profiles of etoricoxib 60/90 mg and diclofenac 150 mg. Results are consistent with a thrombotic risk associated with use of etoricoxib and diclofenac, which is more or less constant over time of exposure, at least up to about 2 years. However, cardiorenal events such as oedema, hypertension and cardiac failure were more frequent and severe with etoricoxib, and this may have indirect relevance to long-term thrombotic event rates. Etoricoxib appeared to offer some gastrointestinal safety/tolerability advantage, but the advantage was not as striking as that seen in previous trials involving higher than licensed doses of some other Cox-2 inhibitors, and it did not extend to all types of events (especially not to 'complicated' events and upper gastrointestinal haemorrhages). Moreover, in patients taking aspirin/anti-platelet agents the advantage was markedly reduced, if not eliminated.

With the available analyses it is not possible to clearly quantify the balance of gastrointestinal benefit versus cardiorenal risk, for etoricoxib versus diclofenac. However, in the MEDAL study alone overall discontinuation rates for all serious adverse experiences were greater for etoricoxib than for diclofenac. Further examination of the final MEDAL data will be important in order to fully examine the cardiovascular comparisons, further subgroups in relation to dose and indication, and more clearly identify the groups that gain most/least from etoricoxib's gastrointestinal profile.

See discussion for diclofenac below.

- TARGET

The TARGET trial was an international, multicentre, randomised, active-controlled, double-blind, double-dummy, parallel group study stratified by low-dose ASA use and age, in patients with osteoarthritis treated for 52 weeks. The study consisted of two sub-studies with identical designs but using different comparators: Lumiracoxib 400 mg once daily was compared to naproxen 500 mg twice daily in study 0117, and to ibuprofen 800 mg thrice daily in study 2332.

In the previous Cox-2 review procedure, the following was concluded:

There was little evidence of increased thrombotic cardiovascular risk over 12 months of use for lumiracoxib compared with ibuprofen, and some evidence to suggest a nonsignificant increase in cardiovascular risk with lumiracoxib compared with naproxen. Lumiracoxib had a better blood pressure (BP) profile than either ibuprofen or naproxen in TARGET. Lumiracoxib had a better gastrointestinal profile than either ibuprofen or naproxen in non-users of low-dose aspirin, and may therefore be a useful short-term treatment for osteoarthritis in patients not using low-dose aspirin. The gastrointestinal benefit for patients taking low-dose aspirin has not been demonstrated. Lumiracoxib treatment may not be appropriate for this subset of patients, in terms of gastrointestinal risk, and particularly since any patients using low-dose aspirin are likely to have existing cardiovascular risk factors. As the effects of lumiracoxib have not been studied for more than 12 months in any patient, there would be an argument for not prescribing lumiracoxib for a period of more than 12 months.

TARGET is a large study, providing valuable results on safety up to 1 year for lumiracoxib compared with ibuprofen and naproxen. However, the lack of a placebo comparison, as well as the fact that high, or supratherapeutic doses, were used for all compounds, complicate the interpretation of the results.

In the presentation of patient baseline characteristics (cardiovascular risk patients), the two substudies (for naproxen and for ibuprofen) were pooled. It seems that the lumiracoxib and NSAIDs groups were balanced (although there was slightly more high risk patients in the lumiracoxib group), but a presentation for each substudy would have been valuable. Such information may be needed to understand why there was a difference in the cardiovascular event rates for lumiracoxib in the two substudies.

There is a higher cardiovascular risk with increasing age and also in male patients. However, the relative or absolute risk for lumiracoxib compared to naproxen/ibuprofen does not seem increased in these patients. Analyses in patients with other risk factors (diabetes, hyperlipidemia, smoking, history of cardiovascular events, etc) have not been presented.

There is some support for the hypothesis that ibuprofen may have an adverse interaction with ASA considering the endpoints myocardial infarction, stroke and APTC[7] (Anti Platelet Trialists' Collaboration) (See below on Ibuprofen and interaction with ASA). For naproxen, there is less clear evidence for an interaction with ASA.

1.4.3.2 Populations at risk

It is estimated that, based on the current data, an increased thrombotic risk with Cox-2 inhibitors would possibly account for 3/1000 events per year, mainly relating to myocardial infarction, but also possibly extending to cerebrovascular and peripheral vascular events. While the thrombotic risk with Cox-2 inhibitors might account for 3/1000 events per year in general, the increased risk is different in patients with and without history of cardiovascular events, depending on their baseline risk. In the APC/PreSAP study (celecoxib vs. placebo), it was seen that patients with a history of prior cardiovascular diseases were at greater risk of cardiovascular events than patients with no cardiovascular history. Although there was no evidence of a significantly different relative risk between patients with or without risk factors, the absolute risk of celecoxib is greater in patients with a

[7] Composite endpoint

history of cardiovascular events (≈ 15/1000 events per year) than in patients without such a history (≈ 2.7/1000 events per year). Similarly, the increased risk for selected cardiovascular thromboembolic events with celecoxib is also greater in patients with history of atherosclerotic heart disease (30/1000 events per year) than in those without it (5/1000 events per year). Therefore, it is important to communicate the cardiovascular risk in patients with different cardiovascular risk factors and the contraindication added to the Cox-2 inhibitors during the previous review procedure seems justified.

1.4.3.3 Dose and Duration of Exposure

Most evidence now suggests that dose-related harmful effects may manifest early and persist throughout treatment, although it is possible that the risk increases with prolonged treatment. Data from APPROVe (for rofecoxib) suggest that the risks may persist for some months beyond cessation of therapy, but no firm conclusions can be drawn, and the relevance of this for other Cox-2 inhibitors /NSAIDs remains unknown.

1.4.3.4 Epidemiological studies

A number of epidemiological data sources have been reviewed. The main ones can be summarised as follows:

- An updated meta-analysis (Medicines and Healthcare products Regulatory Agency meta-analysis, not yet published) of the results of published epidemiological studies relating to the risk of myocardial infarction associated with NSAIDs was performed. Data were analysed for diclofenac, ibuprofen and naproxen, with the following results.

  - The data for ibuprofen prescription showed significant heterogeneity. The pooled relative risk of 1.11 (1.01-1.22) indicates a small increase in the risk of myocardial infarction amongst users of ibuprofen compared to non users.
  - Similarly, the data for naproxen showed significant heterogeneity. The pooled relative risk of 1.02 (0.92-1.13) suggested neither an increased nor decreased risk of myocardial infarction amongst naproxen users and non users.
  - For diclofenac, no significant heterogeneity was detected. The pooled relative risk of 1.35 (1.24-1.47) indicated an increased risk of myocardial infarction amongst users of diclofenac compared with non users.

- GPRD study (unpublished). The cohort design allowed the authors to examine the pattern of risk according to duration of therapy. The findings of increased risk of cardiovascular events for Cox-2 inhibitors are in line with previous studies. 'Frequent current' NSAID use was also associated with an increased risk of myocardial infarction compared to short-term use or non-use (although risks were slightly less than for Cox-2 inhibitors). The magnitude of relative risks for individual products (generally 1-1.5 versus non-use) are in line with other epidemiological studies, although unlike most epidemiological studies, it is notable that the risk estimates for naproxen, ibuprofen and diclofenac were quite similar in this study. The authors consider that confounding by disease severity may be a factor in these results, as the risks persisted several years after discontinuation.

- A nested case-control study by Levesque and colleagues (2006) based on data from the Quebec computerised health database examined the timing of myocardial infarction associated with rofecoxib and celecoxib usage. The results indicated an increased risk for rofecoxib within the period of first prescription (RR=1.67 [1.21-2.30]) than in subsequent prescriptions (RR=1.17 [0.98-1.43]). Only non-significant increases in risk were observed for celecoxib. Methodological issues relating to the differing proportions of switch patients for rofecoxib and celecoxib may have affected the results of this study. Overall, results suggesting an immediate increase in risk with rofecoxib that wanes with persistent treatment is out of line with the randomised clinical trial data.

- Jick et al. (2006). This study used the UK General Practice Research Database (GPRD) to examine the risk of myocardial infarction (MI) in NSAID and Cox-2 inhibitor users, who had "no prior recorded clinically important risk factors for MI". The methodology of this study is unusual and raises a number of questions, especially in relation to incomplete exclusion of risk factors, interpretation of odds ratios in patients who switched therapies and timing of exposure relative to events. However, the authors' conclusion that extensive use of rofecoxib, celecoxib and diclofenac increase the risk of myocardial infarction, but that use of naproxen or ibuprofen do not, remain close to the general pattern seen in other epidemiological studies.

- Lewis et al. (2006). Three recent epidemiological studies in the US, Canada and UK sought to compare the risk of myocardial infarction with meloxicam and other NSAIDs, relative to diclofenac. Limited details are available, however the results showed lower estimates of risk for meloxicam than diclofenac in 2 studies (one reaching statistical significance) and a higher rate (not statistically significant) in the third study (see further discussion on meloxicam).

- A recently published meta-analysis by McGettigan et al. (2006), was based on 17 case-control and 6 cohort studies. It presented similar results as in previous meta-analyses: i.e. a dose-dependent increase of the risk of myocardial infarction for rofecoxib, no association for celecoxib, an increased risk for diclofenac, no changes in the risk for naproxen, piroxicam and ibuprofen. It is noteworthy that the data from the underlying studies regarding diclofenac were consistent whereas the data for naproxen and ibuprofen were heterogenous. When looking at individual studies, some show an increased risk also for naproxen and ibuprofen (Helin-Salmivaara et al., 2006; Hippisley-Cox, 2005; Johnsen, 2005). The finding that celecoxib was not associated with an increased risk in the two meta-analyses by Hernandez-Dias and McGettigan is also noted. It may be explained by predominant use of a lower dose (200 mg daily) or other special exposure characteristics in the underlying studies.

Overall, it appears that diclofenac (150 mg) is associated with a slightly higher risk (both across and within studies) compared to ibuprofen and naproxen. Even if supported by data from clinical trials, caution is due in the interpretation on the causal role of diclofenac for the risk of coronary heart disease; the level of relative risk increase is modest (1.5 or lower), meaning that it could be explained by uncontrolled confounding or bias in the data. For other less selective or non-selective NSAIDs, data on thrombotic cardiovascular risk are clearly insufficient. There are no conclusive data on the possible differential risks of any NSAID in subgroups of patients with regard to age, gender or risk factors, as well as regarding the risks according to duration of use, or dose.

Separate updated analyses of epidemiological data have examined the possible interaction between ASA and ibuprofen/naproxen, which could potentially result in a reduction in the protective anti-platelet effect of ASA. The available data remain inconclusive, with most epidemiological evidence failing to support clinically important interactions.

1.5 Discussion of relevant data for each substance

1.5.1 Cox-2 Inhibitors

The most recent data from PreSAP/APC confirm and strengthen the previous concern regarding increased risk for thrombotic cardiovascular events with celecoxib compared with placebo. Furthermore, subjects with risk factors are at an even higher absolute risk. Data from the MEDAL programme can neither confirm nor reject such concern for etoricoxib, as a placebo comparison is lacking. Taking the data overall there is no suggestion that the risk is any lower than it was perceived when the review was finalised in June 2005. On the contrary, the new data support the previous assessment and thus support that the specific contraindications and warnings introduced during the review regarding thrombotic cardiovascular risk should remain.

In terms of other safety concerns, each respective product already has specific warnings reflecting the individual characteristics of the product (e.g. cardiorenal for etoricoxib; hepatic for lumiracoxib, skin for celecoxib and parecoxib). The European marketing authorisation for valdecoxib (Bextra) is currently suspended.

In terms of gastrointestinal benefit of Cox-2 inhibitors versus non-selective NSAIDs, there are data indicating a better overall tolerability for Cox-2 inhibitors, while data from e.g. the MEDAL programme (etoricoxib vs. diclofenac) and CLASS (celecoxib vs. ibuprofen or diclofenac) show no significant benefit of the Cox-2 inhibitors for "complicated" gastrointestinal events, particularly in patients taking aspirin/anti-platelet agents. Although most evidence suggests a gastrointestinal benefit for Cox-2 inhibitors, further data are needed.

It is concluded that the current SPCs are sufficient to address the safety aspects of celecoxib and etoricoxib, although they should reflect the final APC/PreSAP and MEDAL data (when the final reports will be made available for assessment), for the respective compounds. The final labelling for lumiracoxib has been agreed recently at the level of the Co-ordination group for Mutual recognition and Decentralised procedures – Human (CMDh).

1.5.2 Non-selective NSAIDs

1.5.2.1 Diclofenac

The main reason for the current review are new data from the MEDAL programme suggesting that the overall thrombotic risk for diclofenac (150 mg daily) and etoricoxib (60 or 90 mg daily) is similar. However, there are several issues, which need to be further analysed before the results of the programme can be considered conclusive (e.g. review of individual studies, subgroups, risk factors, dose effects). In addition, there are limitations with this large data set that make firm conclusions difficult. The lack of a placebo group makes the outcome difficult to interpret. Are we observing no increased risk at all, similar increased risk for etoricoxib and diclofenac, or is the design incapable of detecting differences? The interpretation of the outcome is further complicated by the fact that the highest recommended dose of diclofenac was compared with a mixture of data from either the highest recommended dose for etoricoxib or a lower dose. Thus, it has to be acknowledged that despite further analyses of the MEDAL programme being warranted, it may not be possible to draw firm conclusions.

In the CLASS trial, celecoxib (400 mg BID, 2-4 times the authorised dose), ibuprofen (800 mg TID) and diclofenac (75 mg BID) were studied for up to 15 months in RA and OA patients. There was no significant difference in the percentage of patients with serious cardiovascular thromboembolic adverse events for celecoxib (1.3% of patients) versus diclofenac (1.4% of patients) or ibuprofen (1.1% of patients), but the rate of myocardial infarction was higher for celecoxib (0.5%) than diclofenac (0.2%). The total number of events in the trial was low.

There are no other clinical trials of sufficient size and/or duration which can contribute more data regarding thrombotic risk of diclofenac.

Three independent meta-analyses of data from epidemiological studies, and a publication by McGettigan (2006), suggest an increase in the thrombotic cardiovascular risk with diclofenac, particularly when used at daily dose of 150 mg. However, the result should be interpreted with caution since the magnitude of the risk increase is relatively low, and residual confounding on account of disease/severity or other biasing factors which may explain part of the association. Further, there are no consistent data of a dose-risk relationship or differential risk in subgroups of patients with regard to risk factors for cardiovascular disease, age or concomitant use of ASA. It may be noted for other NSAIDS (naproxen and ibuprofen) that even if the associations in corresponding meta-analyses were null or of lower strength, the underlying data were heterogenous. Thus, in some studies all most commonly used non-selective NSAIDs were associated with an increased risk of cardiovascular disease.

Although the mechanism behind an increased thrombotic cardiovascular risk for Cox-2 inhibitors is unclear, degree of Cox-2 selectivity has been put forward as one possible factor. Diclofenac is regarded as having moderate Cox-2 selectivity, which would support the view that its thrombotic cardiovascular risk profile is closer to that of the Cox-2 inhibitors, than e.g. naproxen, which has a Cox-1 preferential profile. However, it is possible that also other factors, e.g. effects on blood pressure, as well as pharmacokinetic differences, also play an important role.

It is concluded that current data point towards diclofenac having a thrombotic cardiovascular safety profile closer to the Cox-2 inhibitors, than naproxen. High dose ibuprofen may also be associated with thrombotic risk, while data for other NSAIDs are insufficient. However, there are currently too many uncertainties and the data are not sufficiently robust to conclude that the thrombotic cardiovascular risk with diclofenc is of the same magnitude as perceived for the Cox-2 inhibitors. It also has to be acknowledged, that the level of risk may differ among Cox-2 inhibitors as well.

Further analyses of the MEDAL programme may provide insights to some of these uncertainties.

From the cardiorenal perspective, diclofenac was seen to have a similar profile to high dose celecoxib in CLASS but a favourable profile compared to etoricoxib in the MEDAL programme.

1.5.2.2 Ibuprofen

The available data on the cardiovascular safety of ibuprofen continue to produce inconsistent results. Data from individual large trials employing 2400 mg ibuprofen daily, together with the metaanalysis by Kearney et al. (2006) have suggested that high doses of ibuprofen may pose similar thrombotic risks to the Cox-2 inhibitors. A further notable point from some of these clinical trials is the relatively adverse pattern of cardiorenal effects seen at doses of 2400 mg daily. As with etoricoxib, it seems likely that these effects would contribute indirectly to any long-term thrombotic risk. However, the epidemiological data have been quite heterogeneous in relation to myocardial infarction, and the point estimate from a recent meta-analysis (Medicines and Healthcare products Regulatory Agency meta-analysis, not yet published) (risk relative to no treatment of 1.11 (95% CI:1.01-1.22) is suggestive of a smaller risk than seen in clinical trials. Overall, for low dose ibuprofen (e.g. less than or equal to 1200 mg daily), epidemiological studies do not suggest an increased risk of myocardial infarction.

Interaction between ibuprofen and acetylsalicylic acid (ASA)

There is some evidence from clinical trials consistent with an interaction between ibuprofen (high dose) and ASA; leading to higher thrombotic risk. There are also a number of clinical pharmacological studies showing that ibuprofen interferes with the anti-platelet effect of ASA (e.g. Catella-Lawson et al., 2001).

In Table 4, the thrombotic event rates in the CLASS study stratified by ASA usage are shown. Data from the TARGET study, stratified for ASA use are shown in Table 5.

CLASS

Table 4 Thromboembolic event rates in CLASS, stratified by aspirin usage

	Ibuprofen 800 mg tid		**Diclofenac 75 mg bd**		**Celecoxib 400 mg bid**	
	Number of patients	Cases (incidence)	Number of patients	Cases (incidence)	Number of patients	Cases (incidence)
thromboembolic events – **all patients**	1,985	21 (1.06%)	1,996	28 (1.40%)	3,987	52 (1.3%)
thromboembolic events – **non-ASA users**	1,573	7 **(0.4%)**	1,551	16 **(1.0%)**	3,105	25 **(0.8%)**
thromboembolic events – **ASA users**	412	14 (3.4%)	445	12 (2.7%)	882	27 (3.06%)
Relative risk [95% CI] ASA users vs. non-ASA users						
	7.64 [3.1;18.8]		2.61 [1.25;5.48]		3.8 [2.22;6.52]	

TARGET

Table 5 myocardial infarction (MI), stroke and APTC in TARGET stratified by aspirin usage

	Ibuprofen 800 mg tid		**Lumiracoxib 400 mg qd**	
	patients	Case (incidence)	patients	Cases (incidence)
MI – non-ASA	3,431	5 (0.21%)	3,401	4 (0.16%)
MI – ASA	966	2 (0.30%)	975	1 (0.14%)
Stroke – non-ASA	3,431	2 (0.06%)	3,401	6 (0.18%)
Stroke – ASA	966	4 (0.41%)	975	2 (0.21%)
APTC – non-ASA	3,431	13 (0.38%)	3,401	13 (0.38%)
APTC –-ASA	966	10 (1.04%)	975	6 (0.62%)
	Naproxen 500 mg bid		**Lumiracoxib 400 mg qd**	
	patients	Case (incidence)	patients	Cases (incidence)
MI – non-ASA	3,537	4 (0.15%)	3,549	18 (0.49%)
MI – ASA	1,193	6 (0.67%)	1,192	8 (0.91%)
Stroke – non-ASA	3,537	6 (0.17%)	3,549	6 (0.18%)
Stroke – ASA	1,193	5 (0.42%)	1,192	9 (0.76%)
APTC – non-ASA	3,537	14 (0.47%)	3,549	22 (0.62%)
APTC –ASA	1,193	13 (1.09%)	1,192	18 (1.51%)

Currently, data from clinical trials suggest that a high dose of ibuprofen (2400 mg daily), has a small increased risk for thrombotic cardiovascular events, while epidemiological data are heterogeneous in relation to myocardial infarction, and suggest a smaller risk than seen in clinical trials. No firm conclusion can be reached regarding explanations for the differing results, but the following factors may have contributed:

- In clinical practice, which is reflected in epidemiological studies, ibuprofen is generally used at much lower doses than the 2400 mg daily used in large Cox-2 inhibitor comparator trials (typically ≤ 1200 mg daily). Overall, the epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤1200 mg daily) is associated with an increased risk of myocardial infarction.
- Unlike naproxen and diclofenac, ibuprofen is not often used to treat severe/inflammatory arthritis (especially rheumatoid arthritis) in clinical practice, and it is likely that such severe/inflammatory arthritis is likely to be an independent risk factor for myocardial infarction.

Furthermore, the results of clinical trials and epidemiological studies may have been affected by the potential interaction with ASA, which has been seen in experimental studies. Further, in CLASS, and to a lesser extent in TARGET, there are trends for a disproportional increase of thrombotic events in ibuprofen + ASA users (relative to ibuprofen alone) compared with NSAID/Cox-2 inhibitors + ASA users vs. NSAID/Cox-2 inhibitors alone, although the number of cases is relatively small. Thus, an adverse interaction between ibuprofen and ASA cannot be excluded based on clinical studies.

Although the clinical implication of the interference by ibuprofen on the anti-platelet effect of ASA is unclear, it is potentially important because the cardioprotective effect of ASA, when used for secondary prevention of myocardial infarction, could be decreased or negated.

1.5.2.3 Meloxicam

New data comprising the final report of three epidemiological studies on the risk of myocardial infarction have recently become available. These data were presented during the 22nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management, held in August 2006 in Lisbon.

Two comparisons have been performed: meloxicam with diclofenac in one report, and meloxicam with non-use in another report.

Three databases in three different countries were used:

- the GPRD (General Practitioner Research Database) in the UK, based on data from general practitioners (GPs). It contains information on 9 million patients (3 million current) and 400 general practices;
- the RAMQ (Règles de l'Assurance Maladie au Québec), based on hospital cases and covering 7.4 million patients on 01/07/04;
- the VA (Veteran's Administration) in the USA, based on hospital cases. It cares for over 7 million patients who have served in the armed forces of the US.

New epidemiological data for meloxicam, based on analyses in three independent databases, do not indicate that meloxicam is associated with an increased risk of thrombotic cardiovascular disease, in relation to non-use or to use of diclofenac. However, the data are rather inconsistent as regards outcomes for other NSAIDs and there are no details on the duration or dose of use or of time to event. Therefore, these new data, although reassuring, do not permit firm conclusions to be made. Thus, there is still uncertainty about the thrombotic cardiovascular risk profile for meloxicam.

1.5.2.4 Naproxen

Data from previous large clinical trials (VIGOR, TARGET), pooled analyses of clinical trials conducted by Marketing Authorisation Holders, and the published meta-analysis by Kearney and colleagues (2006) all suggest that use of naproxen (typically 1000 mg daily) is associated with significantly less long-term cardiovascular risk than that associated with Cox-2 inhibitors. Only the preliminary results of the ADAPT study, which employed a low dose of naproxen (220 mg BID) appears to contradict this trend. Likewise, meta-analysed epidemiological evidence points towards no increased risk of myocardial infarction with naproxen, which contrasts with data from Cox-2 inhibitors. However, some epidemiological studies indicate that thrombotic cardiovascular risk may be increased also for naproxen. In the available meta-analyses of epidemiological studies (e.g. Hernandez-Diaz, 2006; McGettigan, 2006), the pooled risk estimates for naproxen were close to unity; however, the underlying study results were heterogeneous. When reviewing the individual studies, data in the studies e.g. by Helin-Salmivaara (2006), Hippisley-Cox (2005) and Johnsen (2005), indicate that naproxen (or Cox-unselective NSAIDs) may be associated with an increased risk. This heterogeneity in results may reflect important differences in the characteristics of exposure (dose, duration) or the treated populations (type of indication), among studies. As with ibuprofen, there is some mechanistic evidence to indicate that naproxen might interact with aspirin, however there is very little clinical evidence in this regard. A cardioprotective effect, which has been discussed previously, has little or no support in available studies. Thus, there remains uncertainty as regards the risk profile of naproxen.

In relation to cardiorenal effects, naproxen was associated with a lower rate of effects than high dose rofecoxib (50 mg) in VIGOR, but a higher rate of adverse effects than high dose lumiracoxib (400 mg), in TARGET.

Regarding gastrointestinal safety, it seems possible that naproxen may present a higher risk than diclofenac and ibuprofen, although evidence for drawing such conclusion is weak.

1.5.2.5 Etodolac

New data consist of updated epidemiology information, comprising data from a publication (Helin-Salmivarra et al., 2006) of a Finnish matched case-control study, which identified an adjusted odds ratio (OR) for first myocardial infarction of 1.35 (95% CI: 0.44 – 4.17) with current use of etodolac. However, there are still insufficient data to conclude on thrombotic risk for etodolac.

1.5.2.6 Ketolorac

No new data have emerged that alter the previous conclusions.

1.5.2.7 Ketoprofen

There are no data that alter the previous conclusions regarding ketoprofen. There are still insufficient data to conclude on thrombotic risk for ketoprofen.

1.5.2.8 Indomethacin

No new data have emerged that alter the previous conclusions. There are still insufficient data to conclude on thrombotic risk for indomethacin

1.5.2.9 Nabumetone

No new data have emerged that alter the previous conclusions. There are still insufficient data to conclude on thrombotic risk for nabumetone.

1.5.2.10 Nimesulide

There are no new data for nimesulide. There are still insufficient data to conclude on thrombotic risk for nimesulide.

1.5.3 Conclusions on non-selective NSAIDs

The CHMP, having considered the matter as set out in this assessment report, is of the opinion that no public health concerns have been identified that are of Community interest, which would warrant an Article 31 referral. However, the CHMP agrees that the recommendations for use of non-selective NSAIDs should adequately reflect the current level of knowledge on thrombotic risk. To this effect, the CHMP has recommended that its Pharmacovigilance Working Party consider whether there is a need to revise the previously agreed key elements[8] related to cardiovascular safety.

With respect to gastrointestinal and other safety concerns, the key elements agreed in October 2005 are considered sufficient.

2 OVERALL CONCLUSIONS AND RECOMMENDATIONS

The reason for this review under article 5(3) is new data and analyses stemming from clinical and epidemiological studies, which signal a potentially increased arterial thrombotic risk (such as myocardial infarction or stroke) for non-selective NSAIDs, especially when used at high doses and in long-term treatment. These new data include (i) the MEDAL clinical trial programme comparing

[8] Adopted key elements for the prescribing information of non-selective NSAIDs published in October 2005 and adopted key elements for prescribing information of the non-selective NSAIDs piroxicam, ketoprofen and ketorolac published in September 2006

etoricoxib and diclofenac, (ii) updated meta-analyses of clinical and epidemiological studies of NSAIDs and Cox-2 inhibitors, (iii) new epidemiological data for meloxicam (iv) updated analyses for Cox-II inhibitors from the APPROVe, APC and PreSAP studies. The CHMP has reviewed these data sets taking into account previous NSAIDs and Cox-2 inhibitor reviews.

The CHMP agrees the following on the arterial thrombotic risk:

- Data from the MEDAL programme indicate that the overall thrombotic risk for diclofenac (150 mg daily) and etoricoxib (60 or 90 mg daily) is similar. However, there are issues that need to be further analysed before the results of the programme can be considered conclusive (e.g. review of individual studies, subgroups, dose effects). When the full data set is available, these issues will be further assessed.

  Taking all available clinical trial and epidemiological data into account, diclofenac, particularly at a high dose (150 mg daily), may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

- Clinical trial data suggest that ibuprofen at a high dose (2400 mg daily) may be associated with an increased risk of thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤1200 mg daily) is associated with an increased risk of myocardial infarction.

- Clinical trial and epidemiological data suggest that naproxen (1000 mg daily) may be associated with a lower risk for arterial thrombotic events than Cox-2 inhibitors, but a small risk cannot be excluded. Overall, the data do not support a cardioprotective effect.

- For all other non-selective NSAIDs, there are insufficient data to conclude on thrombotic risk. Therefore, an increased risk cannot be excluded.

New epidemiological evidence and updated clinical trial data (APC, PreSAP, APPROVe and meta-analyses) continue to point towards an increased thrombotic risk with Cox-2 inhibitors compared to non-use (in epidemiological studies) and compared to placebo (in clinical studies) possibly accounting for about 3 extra events per 1000 patient-years. This relates mainly to myocardial infarction, and includes cerebrovascular and peripheral vascular events in some studies. For the majority of patients, the potential increase in thrombotic risk is small. However, in subjects with pre-existing risk factors for cardiovascular disease or history of cardiovascular disease, the risk may be higher.

After review of all data currently available to the CHMP, the Committee concludes:

- Non-selective NSAIDs are important treatments for arthritis and other painful conditions.
- It cannot be excluded that non-selective NSAIDs may be associated with a small increase in the absolute risk for thrombotic events especially when used at high doses for long-term treatment.
- The overall benefit-risk balance for non-selective NSAIDs remains favourable when used in accordance with the product information, namely on the basis of the overall safety profile of the respective non-selective NSAID, and taking into account the patient's individual risk factors (e.g. gastrointestinal, cardiovascular and renal).
- Based on this latest review, no public health concerns have been identified that are considered as being of Community interest, which would warrant an Article 31 referral.
- The CHMP agrees that the recommendations for use of the above compounds should adequately reflect the current level of knowledge on thrombotic risk.
- The CHMP recommends that the Pharmacovigilance Working Party should consider whether there is a need to revise previously agreed key elements related to cardiovascular safety for the non-selective NSAID prescribing information.
- The complete results from the MEDAL programme should be analysed in depth when available. Following these analyses, the current recommendations on the cardiovascular safety of Cox-2 inhibitors may be reconsidered.
- Possibilities for further epidemiological studies to obtain additional data on pertinent safety aspects of non-selective NSAIDs will be explored by a joint ad hoc group between the CHMP and the PhVWP.

The CHMP agrees that the general prescribing advice and the advice to patients for NSAIDs remains as follows:

- Prescribers and patients should continue to use NSAIDs at the lowest effective dose for the shortest possible duration to control symptoms.
- Prescribers should continue to select any NSAID on the basis of the overall safety profile of the product, as set out in the product information, and the patient's individual risk factors.
- Prescribers should not switch between NSAIDs without careful consideration of the overall safety profile of the products and the patient's individual risk factors, as well as patient's preferences.

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