

VIOXX: A Scientific Review

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Many media reports have appeared regarding Vioxx since Merck & Co., Inc. reported the results of the APPROVe trial and withdrew Vioxx from clinical use. Some reports cited e-mails from me to Merck Research Laboratory scientists after the VIGOR trial data became available. This document is intended to chronicle the history of the discovery and development of Vioxx in a more complete way than discussed in these media reports.

Nothing has been more important to the Merck Research Laboratories or to me than the safety of patients who take our medicines. Anyone who has worked with me during my time as President of MRL knows that to be a fact. Media reports have questioned the integrity of those physicians and scientists who worked on the discovery and development of VIOXX. I feel compelled to bring to light the data we relied on in making our decisions and how our actions were consistent with the data available at the time. This paper will review the scientific thinking of MRL scientists and many scientists in the academic community who published papers on the subject throughout the course of the VIOXX project from its inception. The paper reviews: (1) why a COX-2 selective inhibitor was made; (2) how clinical studies addressed its development; (3) the thought process behind the VIGOR trial; (4) MRL's immediate response to the data from VIGOR; (5) the rapid public dissemination of the data; (6) the FDA approved label for VIOXX incorporating the data from the VIGOR trial; (7) the scientific data and debate between the release of the VIGOR data and the APPROVE trial that led to the withdrawal of VIOXX, a decision made nearly two years after I stepped down from being President of MRL.

In 1993, after a scientific meeting in Keystone, Colorado, the Merck Research Laboratories began a program to make a selective inhibitor of COX-2. Scientific reports at that meeting had revealed that there were two isoforms of cyclooxygenase. COX-1 was present normally in the gastrointestinal tract and COX-2 was induced in inflammatory cells at sites of inflammation. Although all the mechanisms by which traditional NSAIDs caused gastrointestinal ulcers were not known, inhibition of COX-1 in the stomach and duodenum was the prevailing scientific thought on how traditional NSAIDs caused gastrointestinal ulcers in humans. The new information suggested that a

selective COX-2 inhibitor would have enhanced safety for the GI tract compared to traditional NSAIDs and retain the efficacy of traditional NSAIDs. The project proceeded rapidly due to the dedication of scientists at the Merck Frosst Laboratories and in 18 months we had development candidates. One of these turned out to be VIOXX.

In initial clinical studies, VIOXX was shown to alleviate dental pain, thus showing for the first time in humans that a COX-2 selective inhibitor had efficacy. Initial gastrointestinal endoscopy studies demonstrated that as much as 250 mg of VIOXX once a day for 7 days in 51 subjects produced many fewer ulcers than 2400 mg of ibuprofen. 2400 mg/day is the highest dose of ibuprofen approved in its label. At the time we thought the clinical dose of VIOXX might need to be as high as 100 mg. When we learned later than the usual dose was 12.5 mg, we were clearly excited and looked forward to future endoscopy studies after longer exposure to VIOXX at lower clinical doses.

We performed clinical efficacy dose finding studies with great care. Since we now had data in humans to suggest enhanced safety on the GI tract, we paid particular attention to VIOXX's effect on kidney function. Traditional NSAIDs can adversely affect salt and water balance and elevate blood pressure in patients, and it was not known in humans what effect selective inhibition of COX-2 would have on renal physiology and blood pressure. If VIOXX did, in fact, have enhanced GI safety vs. traditional NSAIDs, we did not want physicians to try higher doses than were also safe for kidney function and blood pressure in patients whose pain and inflammation were difficult to treat. We determined the clinical dose for osteoarthritis would be 12.5 mg, with some patients gaining extra benefit from the maximum dose of 25 mg. 50 mg was found to be an optimal dose for relief of acute pain and primary dysmenorrhea. Studies on salt and water balance indicated 12.5 mg and 25 mg were appropriate for chronic use. When the drug was initially approved, the label for osteoarthritis stated clearly the “recommended starting dose of VIOXX is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.”

During the Phase III development program, studies were performed to assess and prove in humans that the doses to be used chronically (12.5 mg and 25 mg) were actually safer with regards to gastrointestinal ulcers. Special studies were also done to assess safety for the small intestine since it was known that NSAIDs historically could also cause small intestinal problems in humans. The

studies on the small intestine were carefully done and were consistent with our hypothesis that this drug would not cause small intestinal ulcers.

The endoscopy studies were especially demanding and extensive. The data were obtained from two replicative studies with 689 patients in one study and 738 patients in another study. This data was included in the initial approved label for VIOXX. The results indicated a clear and large difference between the highest approved chronic dose of VIOXX (25 mg) and the highest allowed chronic dose of ibuprofen (2400 mg) over three time intervals (1) a 6-week period which included placebo; (2) a 3-month period which included placebo, and (3) a 6-month period. Because the study was conducted in patients with osteoarthritis, we could not maintain a placebo arm for the second 3 months since osteoarthritis is a painful condition. Not only did the study show the large difference from ibuprofen, but VIOXX was not detectably different in these studies from placebo for ulcers after 3 months of continuous use. Clearly one could not conclude that VIOXX had no risk of causing ulcers. Proving a negative result is always difficult in science. Nevertheless, the enhanced safety for the gastrointestinal tract was clear.

An interesting scientific discussion ensued among scientists and FDA regulatory personnel. It was often said there is no relationship between GI ulcers and the serious complications of NSAIDs such as perforations, obstructions, and bleeding. Thus for MRL to prove that this constellation of complications was reduced in patients taking VIOXX, an outcomes study measuring these events would be needed and required.

I have always thought that that issue should be more clearly articulated. A more accurate statement might have been that no simple quantitative relationship existed between ulcers detected by endoscopy and the triad of serious complications that arise in long clinical use. However, it was inconceivable to me that the pathophysiology process that leads to ulcers detected by endoscopy could not be integrally related to the processes that lead to the triad of more serious complications. To contend that the extensive 6 month endoscopy studies would not predict better long term gastrointestinal safety was simply not scientifically logical.

The next question was how to do such a study. Given the endoscopy data in patients with osteoarthritis, we asked ourselves, "was it ethical to do an outcomes study in such patients comparing

25 mg VIOXX to any NSAIDs?" The FDA wanted the outcomes study done at 50 mg. Was it ethical to do an outcomes study at 50 mg in patients with osteoarthritis vs. any other NSAID given that the highest recommended dose for which Merck sought approval for osteoarthritis was 25 mg once a day? At the time, the studies for rheumatoid arthritis were not completed although data existed that VIOXX had efficacy in RA. We believed the dose was going to be 50 mg although subsequent data showed that 25 mg was the correct dose. Thus it was decided to test 50 mg dose at the insistence of the FDA and to do that in patients with RA where we thought at the time 50 mg would be the dose for this indication. In planning the GI outcomes study, MRL scientists on the project team faced many unknowns and scientific conundrums. Which NSAID to compare to VIOXX was the first question. Ibuprofen was considered but I recall that it was a drug taken 4x day and that compliance in a long term study would therefore be difficult. Diclofenac was considered but I knew it had an incidence of liver function abnormalities and was concerned that such abnormalities might compromise the eventual number of patients in the trial. Eventually, the decision was made to compare VIOXX to naproxen.

Given that the FDA wanted the outcomes study done with 50 mg of VIOXX, MRL scientists pondered what patient population the study could be performed in. At the time available data suggested that 50 mg would be the dose for patients with rheumatoid arthritis, although the clinical trials in patients with RA were not yet complete. It was decided that the only ethical way 50 mg could be studied was in patients with rheumatoid arthritis. (When the trials in RA were completed in 2001, in fact the correct dose was determined to be 25 mg also in the patients with RA.)

The study was begun, and based on the completed large Phase III program, VIOXX was approved on May 20, 1999. Celebrex had already been approved with data from endoscopic studies that showed it produced fewer GI ulcers than comparator NSAIDs but with data far less convincing than the data in the FDA approved VIOXX label. VIOXX was well received in the market as Merck tried to gain market share from Celebrex which had been approved 6 months earlier.

Merck was competing well and gaining market share but had not surpassed Celebrex in early 2000. I was eager to see the data from the GI outcomes study. Not because I was worried about the result, but hoping it would be the data Merck needed to show how much better VIOXX was than Celebrex. I asked the Merck statistician designated to oversee the trial to allow me to see the data the very minute the study was completed. The scientist strongly reminded me that I was not allowed to be

the first and that there was a process and an order as to who would see the data based on prespecified rules. I retreated from my request and fully complied with the process with that reminder and awaited to be called. No one at Merck besides the statistician predesignated by the study protocol had any knowledge of any unblinded data in VIGOR before the study was fully completed.

On March 9, 2000, I was called and was told the results: both the GI outcomes data and the cardiovascular outcomes data. Although clearly pleased at the GI outcomes, I was stunned at the CV data and stated there was a clear effect. I, in fact, thought VIOXX had elevated the CV event rate. Despite my initial thought, I wanted to buoy the spirits of a team that had worked so diligently for so long on this program. My first comments were intended to encourage them to perform an in depth analysis of all the data in the trial since in many past trials first impressions of the interpretation of new data, I knew often were not accurate.

What was the scientific background for my first reaction?

In 1997, in a study sponsored by Merck, there was the surprising discovery that VIOXX, a COX-2 specific inhibitor, reduced the urinary excretion of a prostacyclin metabolite. A separate study had demonstrated similar effects with Celecoxib another COX-2 inhibitor. Prostacyclin is a major product of arachadonic acid metabolism and was considered to be an antiplatelet factor that inhibits platelet aggregation. These metabolite results were totally unexpected; previous studies of vascular tissue, isolated cells and immunohistochemistry suggested that COX-1 was responsible for prostacyclin production. The new finding was interpreted as indicating that COX-2 had a role in systemic prostacyclin synthesis. Both the nonselective NSAIDs and the COX-2 inhibitors may inhibit this pathway. Because selective COX-2 inhibitors do not affect platelet function whereas standard NSAIDs do, it was hypothesized that selective COX-2 inhibitors might alter the balance between the platelet derived thromboxane and the systemic prostacyclin and thereby increase the risk of cardiovascular events. These data were published in 1999. It is important to emphasize that the effect of prostacyclin was only a partial reduction as measured by a metabolite of prostacyclin in the urine. It is also important to realize that the in vivo importance of the reduction in the urinary metabolite was not known but a hypothesis. Studies conducted at Merck Frosst were not able to determine the source in animals of this prostacyclin metabolite. Around this time, data were also emerging that inflammation was a risk factor for athero-thrombosis (CRP levels) and it was postulated that anti-

inflammatory therapies might diminish the risk of cardiovascular events. Thus it was possible that partial reduction in systemic prostacyclin might be a risk factor for patients with cardiovascular disease and also possible that an anti-inflammatory drug might benefit such at risk patients. No data existed to resolve these two alternatives.

The prostaglandin metabolite results had become available to us as we neared completion of the initial development program which evaluated the safety and efficacy of VIOXX in the treatment of patients with osteoarthritis and acute pain (before the VIGOR trial was even started). The data prompted our team to conduct an immediate retrospective review of the cardiovascular thrombotic events in the Phase II and Phase III osteoarthritis studies. This was done first on a blinded basis and again when we had the unblinded data. These studies included 5435 osteoarthritis patients who participated in 8 double-blind, placebo-controlled and active comparator studies. In these studies, there were similar rates of thrombotic cardiovascular adverse events among patients taking VIOXX, placebo, and comparator NSAIDs (ibuprofen, diclofenac, or nabumetone). Thus, the first major studies conducted with VIOXX found **no** difference in cardiovascular thrombotic risks when comparing VIOXX with placebo or the NSAIDs ibuprofen, diclofenac, or nabumetone, even with a careful retrospective analysis. Nevertheless, we decided to prospectively collect and adjudicate all cardiovascular thrombotic events in all future trials of VIOXX to carefully monitor data on the question. This decision was made even before the VIGOR trial was designed. The Phase II and Phase III data were submitted to the United States Food & Drug Administration as part of the New Drug Application for VIOXX, specifically reviewed at a public meeting of the FDA Arthritis Advisory Committee, and later published in Konstam, et al., “Cardiovascular Thrombotic Events in Controlled Clinical Trials of Rofecoxib,” *Circulation*.ⁱ

Thus, when I first saw the VIGOR data, my initial thought was the prostacyclin metabolite data and thus my reaction. The project team then subsequently explained to me that there was another plausible explanation, that naproxen had been cardioprotective. This was a theory based on naproxen’s ability to inhibit COX-1. Despite the rationale for this theory, no one had ever before shown naproxen was cardioprotective. Why? Aspirin could be shown to be cardioprotective with relatively low doses because of two features (1) ASA irreversibly attaches itself to COX-1 in platelets, (2) to generate more platelets with active COX-1, new platelets need to populate the circulation from bone marrow precursor cells, a process which takes considerable time. Platelets existing in the circulation lack

nuclei and cannot simply make new templates for new COX-1 enzyme after residual ASA is cleared rapidly from the bloodstream. This is in contrast to stomach cells which can remake COX-1 rapidly from existing cells after short exposure times to low dose ASA. Thus, ASA can be relatively selective in its effect for platelet COX-1 vs. stomach COX-1. Naproxen taken at 500 mg b.i.d. could also block platelet COX-1 relatively completely because of its potency and long half life in the circulation. But because naproxen inhibits platelet COX-1 reversibly and not irreversibly like ASA, naproxen could not be expected to selectively inhibit platelet COX-1 for a 24 hr period without also inhibiting stomach COX-1 for a 24 hour period, and therefore produce many serious GI side effects. Thus, naproxen could not have been previously studied in a cardiovascular outcomes study like the ones in which ASA had been shown to be cardioprotective. One could speculate on whether Naproxen could be cardioprotective with good logic, but no clinical evidence existed at the time.

In telling me about the naproxen hypothesis, the team cited a paper in which flurbiprofen, a long acting NSAID, had been shown in fact to prevent rethrombosis after cardiac angioplasty and showed me the paper and the data.ⁱⁱ I did not readily accept that explanation. In the next few minutes I asked them to review up to date all other available data from ongoing trials of VIOXX, against all other NSAIDs and placebo. I was disturbed that so little comparison to placebo existed although copious data vs. other NSAIDs was available, none of which showed any CV events for VIOXX different from other non-naproxen NSAIDS. At my intense questioning of the relative paucity of placebo vs. VIOXX data, I was reminded we were studying VIOXX in osteoarthritis and that we could not keep such patients on placebo for long trials because osteoarthritis is a painful condition. Then during that discussion, a team member recalled an ongoing trial in patients with Alzheimer's Disease.

Another hypothesis was extant at the time: Alzheimer's disease had an inflammatory pathological component. If one could block that component, it was hypothesized that one might slow the progression of the disease. (This hypothesis has never been proven to this day in clinical trials.) Thus, we were in the midst of a study in elderly patients with Alzheimer's Disease, some of whom undoubtedly had underlying heart disease. The study design was 25 mg VIOXX, as an anti-inflammatory vs. placebo, an ethical study, since no drug had been shown to arrest or retard the Alzheimer's disease process. A relatively large patient database was available with only 2 arms to the trial, group A and group B. I was told we had blinded records of all adverse experiences which were always reported and promptly recorded during the course of any clinical trial. We could look at CV

events in group A vs. group B. If an imbalance were found, we would totally unblind the data and see if there was evidence vs. placebo that VIOXX was prothrombotic. The team worked incessantly in the next 24-48 hours and they were instructed to call me as soon as the data collection and tabulation was done. We all fully agreed if an imbalance were observed, we would determine if it were in the VIOXX arm or the placebo arm. On a Sunday night at 8:30 p.m., I received a call and was told all the data for total CV events and all available subcategories. There was no difference or pattern of differences between group A or group B. There was no evidence in any trial except VIOXX vs. naproxen in VIGOR that the CV event rate was different for VIOXX vs. placebo or other NSAIDs.

In the next few days, we queried an additional data source. In 1999, we were given a preprint of a case report of a patient with Lupus Erythematosus, an autoimmune disease where excess platelet activation was known to occur. This patient had been switched from a traditional NSAID to Celebrex and had a venous thromboembolism. The prostacyclin data on Celebrex in man was known at this time and the author speculated on a possible role for Celebrex in the patient's venous clot. Thus, we looked at available databases for the number of prescriptions written for VIOXX in patients with Lupus. I was told that despite the fact that there were 30,000 patients for whom VIOXX prescriptions had been written, we had no spontaneous reports of CV events in such patients. Being persistent, I then instructed the team to call a few leading rheumatologists to inquire if any of them had an experience with VIOXX like the case report above. No one had such an experience.

Given the available data, the team and I concluded that it was likely that naproxen had been cardioprotective. Alternative explanations could not be formally excluded, but the explanation appeared to explain all the available data. Flurbiprofen had set the precedent, the group that raised the speculation had, in fact, been prescient, even though to this point in time in March 2000, I had not recalled or was not familiar with their prior deliberations. No clinical data gathered in clinical trials with VIOXX except in the VIGOR trial came to my attention that caused me any concern about CV risk of VIOXX (Additionally, preclinical MRL scientists continued to study VIOXX and were instructed to look for a prothrombotic effect in an animal model that might reveal such. Such studies were later conducted in a subhuman primate complete with positive and negative controls and revealed no prothrombotic effect of either VIOXX or Celebrex.)

What did MRL do with the VIGOR results? We promptly told the FDA of our data and requested an expedited review. Despite the fact that VIGOR was a large trial involving 8,000 patients, we worked as rapidly as possible to submit fully validated data. We did that in just 3 months.

We also wanted to make physicians and patients aware of the results immediately. The naproxen cardioprotective effect appeared to us to be the explanation based on all available data as noted above, and we had excluded the use of ASA from all our trials up to this point in time.

If naproxen had been cardioprotective, then it was important to allow low dose ASA use in patients taking VIOXX in our trials and to make people aware of this in patients taking VIOXX since ASA had been excluded from all our ongoing trials as it had in VIGOR. Such trials including VIGOR, of course, had exclusions for enrolling patients with underlying heart disease. We decided that the fastest way to make all the available data known was to issue a press release and to send a letter to every investigator conducting any trial with VIOXX or Arcoxia. This would occur immediately and thus be broadly known while an FDA submission was prepared and eventually was reviewed. The press release was issued and the investigator letters sent March 27. The documents stated all data from all available trials, pointed out the VIGOR data, put forth the Naproxen cardioprotective hypothesis, stated clearly that such an effect of Naproxen had not been previously observed, changed the trial guidelines now to allow ASA use in patients doctors chose to use ASA in, and explained again the lack of effect of VIOXX on platelet COX-1. Thus, there was wide dissemination with all available data 18 days from the time I knew the data. The FDA had been notified earlier consistent with regulatory requirements.

During this time and continually thereafter, we evaluated the VIGOR data and continued to consider all possible options. In the meantime, the VIGOR results received extensive coverage and were widely debated in the scientific community, in the financial community, and in the press. Merck participated in these scientific discussions by making the data widely and quickly available and explaining the basis for our conclusions. Merck presented the data at Digestive Diseases Week in May and published the study in *The New England Journal of Medicine* in November (Bombardier 2000). An application to include the results in prescribing information was submitted to FDA in June 2000, followed by a public Advisory Committee meeting in February 2001. The prescribing information for

VIOXX was subsequently changed in the United States and around the world to reflect the cardiovascular results of VIGOR.

PRECAUTIONS

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Cardiovascular Effects

The information below should be taken into consideration and caution should be exercised when VIOXX is used in patients with a medical history of ischemic heart disease.

In VIGOR, a study in 8076 patients (mean age 58; VIOXX n=4047, naproxen n=4029) with a median duration of exposure of 9 months, the risk of developing a serious cardiovascular thrombotic event was significantly higher in patients treated with VIOXX 50 mg once daily (n=45) as compared to patients treated with naproxen 500 mg twice daily (n=19). In VIGOR, mortality due to cardiovascular thrombotic events (7 vs 6, VIOXX vs naproxen, respectively) was similar between the treatment groups. (See CLINICAL STUDIES, *Special Studies, VIGOR, Other Safety Findings: Cardiovascular Safety.*) In a placebo-controlled database derived from 2 studies with a total of 2142 elderly patients (mean age 75; VIOXX n=1067, placebo n=1075) with a median duration of exposure of approximately 14 months, the number of patients with serious cardiovascular thrombotic events was 21 vs 35 for patients treated with VIOXX 25 mg once daily versus placebo, respectively. In these same 2 placebo-controlled studies, mortality due to cardiovascular thrombotic events was 8 vs 3 for VIOXX versus placebo, respectively. The significance of the cardiovascular findings from these 3 studies (VIGOR and 2 placebo-controlled studies) is unknown. Prospective studies specifically designed to compare the incidence of serious CV events in patients taking VIOXX versus NSAID comparators or placebo have not been performed.

Because of its lack of platelet effects, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. Therefore, in patients taking VIOXX, antiplatelet therapies should not be discontinued and should be considered in patients with an indication for cardiovascular prophylaxis. (See CLINICAL STUDIES, *Special Studies, Platelets*; PRECAUTIONS, *Drug Interactions, Aspirin.*) Prospective, long-term studies on concomitant administration of VIOXX and aspirin evaluating cardiovascular outcomes have not been conducted.

Fluid Retention, Edema, and Hypertension

Fluid retention, edema, and hypertension have been reported in some patients taking VIOXX. In clinical trials of VIOXX at daily doses of 25 mg in patients with rheumatoid arthritis the incidence of hypertension was twice as high in patients treated with VIOXX as compared to patients treated with naproxen 1000 mg daily. Clinical trials with VIOXX at daily doses of 12.5 and 25 mg in patients with osteoarthritis have shown effects on hypertension and edema similar to those observed with comparator NSAIDs; these occurred with an increased frequency with chronic use of VIOXX at daily doses of 50 mg. (See ADVERSE REACTIONS.) VIOXX should be used with caution, and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or heart failure.

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DOSAGE AND ADMINISTRATION

Osteoarthritis

The recommended starting dose of VIOXX is 12.5 mg once daily. Some patients receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

Rheumatoid Arthritis

The recommended dose is 25 mg once daily. The maximum recommended daily dose is 25 mg.

Management of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended dose of VIOXX is 50 mg once daily. The maximum recommended daily dose is 50 mg. Use of Vioxx for more than 5 days is management of pain has not been studied. Chronic use of VIOXX 50 mg daily is not recommended. (See ADVERSE Reactions, Clinical Studies in OA and RA with VIOXX 50 mg).

Patient Information about VIOXX

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What are the possible side effects of VIOXX?

Serious but rare side effect that have been reported in patients taking VIOXX or related medicines have included:

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- Heart attacks and other serious events, such as blood clots in your body, have been reported in patients taking VIOXX.

On the advice of one of our consultants, to enhance the power and precision of our analyses, we also conducted a pooled analysis of the cardiovascular events from 23 studies involving more than 28,000 patients, representing more than 14,000 patient years. In this analysis, there was no evidence of an increased risk of cardiovascular thrombotic events for VIOXX compared to placebo or VIOXX compared to non-naproxen NSAIDs. There was, however, an increased risk of events on VIOXX compared with naproxen. Because of this difference in findings against the different comparators, we felt that it was inappropriate to combine all the comparator data into a single group even though doing so would have diminished the apparent difference from naproxen. We presented this analysis at major

medical meetings and published it in *Circulation* in October 2001. We provided up-dates to this analysis to regulatory authorities and published an up-dated analysis in the American Heart Journal.

Notwithstanding the extensive amount of clinical data detecting no difference in cardiovascular event rates between VIOXX at the maximum allowed chronic doses 12.5 mg and 25 mg and placebo and VIOXX and non-naproxen NSAIDs, MRL continued to study and monitor the cardiovascular safety of VIOXX. MRL also began evaluating different potential designs to gather CV outcomes data for VIOXX. In December 2001, I announced our intention to perform large outcome studies with VIOXX to further characterize CV risk. MRL was aware of recommendations that this study be performed in high-risk cardiovascular patients. However, this was felt to be problematic (1) because it was not clear what potential benefit to patients could be tested in such a study and (2) because all of the patients in such a study would have needed to take aspirin which could have potentially obscured a prothrombotic effect of VIOXX. After deliberations with numerous consultants, MRL finalized a protocol in 2002 which prespecified the analysis of adjudicated cardiovascular event data from placebo-controlled studies as a hypothesis-testing endpoint. These studies would enroll patients with a spectrum of CV risk, including patients taking and not-taking aspirin. Two of these studies, APPROVE and VICTOR, a 7000 patient study in patients with a history of colon cancer, had begun and the third, a 15,000 patient study in patients at risk for prostate cancer was initiated after consultation with regulatory agencies.

Publications Appearing After Announcement of VIGOR Results in Chronological Order

August 2001 A meta analysis was published in *JAMA* by Mukherjee et al.

The paper attempted a meta analysis of the VIGOR trial and the CLASS trial (for Celecoxib) to compare the relative risk for thrombotic cardiovascular events in these trials to an historical incidence of similar events in various secondary prevention trials testing ASA's effectiveness in reducing myocardial infarction. The comparison was between the historical control groups in the ASA trials to the treated groups in the coxib trials. The authors concluded that the annualized myocardial infarction rates in the coxib trials were significantly higher than in the historical placebo group.

It is noteworthy that the Mukherjee, et al. study used a historical control group to compare to patients using rofecoxib and Celebrex. In studies performed by drug

discovery companies submitted to FDA for approval for inclusion in drug labels, historical controls are simply not allowed. Historical controls are not considered valid in studies claiming new findings about prescription medicines, and meta analyses which use such control groups are not considered statistically valid by the statistical community.

(Mukherjee, D., Hissen, S.E. and Topol, E.J. Risk of Cardiovascular Events Associated with Selective COX-2 Inhibitors. JAMA, 286, 954-959, 2001.

Timeline of Epidemiological Studies Involving VIOXX or NSAIDs

- Nov 2001 The *Medical Letter* reviewed the cardiovascular safety of COX-2 inhibitors. That review concluded, “in one study, high doses of rofecoxib taken for months were associated with a 1.11% incidence of thrombotic cardiovascular events compared to 0.47% with naproxen. Taking aspirin with a selective COX-2 inhibitor could protect against any possible prothrombotic effect, but would probably also diminish the apparent advantage in gastrointestinal safety with these drugs. Until more prospective studies with and without low-dose aspirin are available, it would be premature to conclude that rofecoxib or celecoxib increase the risk of thrombotic cardiovascular disease.”
- Jan 2002 A retrospective cohort study by Ray et al is published in *The Lancet*. Objective was to measure the effects of non-aspirin NSAIDs, including naproxen, on risk of serious coronary heart disease (CHD). The adjusted RR (95% CI) for use of naproxen <1000 mg relative to non-use of any NSAID was 0.83 (0.64, 1.09), while that for ≥1000 mg was 1.00 (0.84–1.18). When use of naproxen was compared with use of ibuprofen, the RR was 0.83 (0.69–0.98). Study concludes that in a high-risk patient population of people 50 years and older, non-selective non-aspirin NSAIDs neither increased nor decreased risk of serious CHD compared with non-use. Analysis evaluated 6,362 cases from the Tennessee Medicaid program during 181,441 periods of new NSAID use in 128,002 people and the same number of periods of non-use of NSAIDs among 134,642 people.
- Ray WA, Stein CM, Hall K, Daugherty JR, Griffin MR. Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study. *Lancet* 2002; 359: 118-23.
- May 2002 Three separate case-control studies are published in *Archives of Internal Medicine*. Each showed that use of naproxen reduced the risk of heart attacks. These studies were

first presented at the American College of Rheumatology meeting in 2001.

Solomon et al: Objective was to determine whether NSAIDs have a similar effect or whether they differ in their effects on the risk of acute myocardial infarction (AMI). Study concludes that the findings do not support a relationship between the use of NSAIDs as a group and risk of heart attacks. However, use of naproxen was associated with a significant reduction in the risk of AMI (adjusted odds ratio, 0.84; 95% confidence interval, 0.72-0.98; $P = .03$). Analysis evaluated 4,425 cases from the N.J. Medicare/ Medicaid Program against a control group of 17,700 subjects.

Solomon DH, Glynn RJ, Levin R, Avorn J. Nonsteroidal anti-inflammatory drug use and acute myocardial infarction. *Arch Int Med* 2002; 162: 1099-1104.

Watson, et al: Objective of the study was to examine the risk of acute thromboembolic cardiovascular events (heart attack, sudden death and stroke) with naproxen use among patients with rheumatoid arthritis. The study concludes that patients with rheumatoid arthritis and a current prescription for naproxen had a reduced risk of acute major thromboembolic CV events relative to those who did not take naproxen in the past year. Analysis evaluated 809 cases from British General Practice Research Database against a control group of 2,285 subjects. Study sponsored by Merck.

Watson DJ, Rhodes, T, Cai B, Guess HA. Lower Risk of Thromboembolic Cardiovascular Events with Naproxen Among Patients with Rheumatoid Arthritis. *Arch Int Med* 2002; 162: 1105-10.

Rahme, et al: Objective of the study was to compare the effect of naproxen to other NSAIDs in the prevention of acute myocardial infarction (AMI) in an elderly population. The study concludes that compared to other NSAIDs, concurrent use of naproxen has a protective effect against AMI. Analysis evaluated 4,163 cases from Canadian RAMQ and Med-Echo databases against a control group of 14,160 subjects. Study sponsored by Merck.

Rahme E, Pilote L, LeLorier J. Association between Naproxen Use and Protection Against Acute Myocardial Infarction. *Arch Int Med* 2002; 162: 1111-5.

Editorial associated with the article: The good news for the millions of users of COX-2 inhibitors (and their manufacturers) is that there is no evidence that use of COX-2 inhibitors increases (or decreases) the risk of myocardial infarction. The findings in the VIGOR study and the findings in the report by Mukherjee et al are readily explicable by the beneficial effects of naproxen rather than a detrimental effect of COX-2 inhibitors.

Many users of NSAIDs and COX-2 inhibitors are in the age group that has or is at risk of having coronary artery disease. Therefore, the concomitant use of low-dose aspirin (80 mg/d) should be strongly considered in patients with a history of coronary artery disease, stroke, transient ischemic attack, or peripheral vascular disease. Aspirin should also be considered in patients older than 50 years who have 1 or more risk

factors for coronary artery disease. Although naproxen reduces the risk of myocardial infarction, it offers less protection than aspirin; therefore, aspirin should be considered in patients at risk of myocardial infarction who are taking naproxen.

Sep. 2002 **Schlienger et al.** published a case-control analysis using the United Kingdom-based General Practice Research Database (GPRD) in the *British Journal of Clinical Pharmacology*. The objective was to examine whether use of non-aspirin NSAIDs may be associated with a decreased risk of first-time acute MI in patients treated between 1992 and 1997. There were 3319 cases and 13,139 controls. The overall adjusted RR for AMI in current NSAID users was 1.17 (95% CI 0.99, 1.37). The adjusted RRs for use of naproxen was 0.68 (0.42-1.13) based on 19 exposed cases and 105 exposed controls. The authors concluded that current NSAID exposure does not decrease the risk of AMI.

Schlienger RG, Jick H, Meier CR. Use of nonsteroidal anti-inflammatory drugs and the risk of first-time acute myocardial infarction. *Br J Clin Pharmacol*. 2002;54: 327–32

Oct 2002 A retrospective cohort study by **Ray et al** is published in *The Lancet*. Objective was to assess occurrence of serious coronary heart disease (CHD), specifically acute myocardial infarction (AMI) and cardiac death, in patients taking Vioxx, celecoxib or other NSAIDs. Study concludes use of Vioxx at doses greater than 25 mg could be associated with an increased risk of serious CHD (based on 12 exposed cases); in contrast, there was no evidence of increased risk among users of Vioxx at doses of 25 mg or less, celecoxib, naproxen or ibuprofen. Analysis evaluated 5,316 events from the Tennessee Medicaid program among 251,046 NSAID users and 202,916 non-users.

Ray WA, Stein CM, Daugherty JR, Hall K, Abrogast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet* 2002; 360: 1071-3.

Oct 2002 A database cohort analysis by **Levy et al** is presented at the American College of Rheumatology meeting. Objective was to assess the correlation between COX-2 use and heart attacks among persons prescribed a COX-2 inhibitor, ibuprofen, or naproxen for at least 50 consecutive days. Study concludes long-term use of either of the COX-2 inhibitors (Vioxx and celecoxib) separately is not associated with an increased risk of heart attack compared with naproxen or ibuprofen. When users of COX-2 inhibitors were combined, there was an increased risk compared with users of ibuprofen or naproxen combined. Analysis evaluated 645 events from the Kaiser Permanente database among 172,260 subjects.

Conclusion: “Long term use of COX-2s in a large staff model HMO is not associated with a significant increased risk of MI when compared to naproxen or ibuprofen. An analysis of the combination of both COX-2s compared to a cohort of NSAIDs showed an OR of 1.3 (95% CI 1.1-1.6). Further analysis is planned to examine the effect of length of exposure, dose effects, OTC NSAID use, smoking and concomitant ASA use on MI risk.”

Levy GD, Cheetham C, Shoor S. Cohort Analysis of Myocardial risk and COX-2 in the Kaiser Large Observational Thrombosis Study (KLOTS). *Arthritis Rheum* 2002; 46 (9 suppl): 5377.

Feb 2003 A population-based, retrospective cohort study by **Mamdani et al** is published in *Archives of Internal Medicine*. Objective was to compare the rates of acute myocardial infarction (AMI) among elderly patients taking COX-2 inhibitors, naproxen and non-aspirin NSAIDs. The rates of MI among the drugs studied were not different from each other nor were any of them different from controls not using NSAIDs. Study concludes no increased short-term risk of AMI among users of COX-2 inhibitors and no short-term reduced risk of AMI with naproxen. Analysis evaluated 701 events from administrative health care databases in Ontario among 66,964 users and 100,000 non-users.

Mamdani M, Rochon P, Juurlink, Anderson GM, Kopp A, Naglie G, Austin PC, Laupacis A. Effect of COX-2 selective cyclooxygenase inhibitors on short term risk of acute myocardial infarction in the elderly. *Arch Int Med* 2003; 163: 481-6.

Nov 2003 A case-control study by **Kimmel et al** is presented at the American Heart Association annual meeting. Objective was to determine the risk of nonfatal heart attacks in users of COX-2 inhibitors compared with users of non-aspirin NSAIDs. Study concludes there was no increased risk of heart attacks overall from COX-2 inhibitors. However, the effects of the two COX-2 inhibitors varied: celecoxib was associated with a reduced risk of MI while Vioxx was not associated with either reduced or increased risk. As a result the difference between them was significant. Nonselective, non-aspirin NSAIDs were also associated with a reduced risk of heart attack. Analysis evaluated 1,718 cases against 6,800 controls from the Delaware Valley Case-Control Network. Study sponsored by Merck and Pharmacia.

Conclusion: “There was no increased risk of MI overall from COX-2 inhibitors detected in this study. However, celecoxib and rofecoxib appear to have different effects, possibly due to a protective effect of celecoxib and a neutral effect of rofecoxib. These effects could explain the findings of randomized trials comparing COX-2s with nonselective NSAIDs.”

Kimmel SE, Berlin JA, Reilly M, Jaskowiak J, Kishel L, Strom BL. Risk of Myocardial infarction by type of cyclooxygenase-2 inhibitor. *Circulation* 2003; 108(17 Suppl IV):IV-752.

June 2004 Garcia-Rodriguez et al published a cohort study with a nested case-control analysis in *Circulation*. The objective was to determine whether use of NSAIDs affected risk of CHD, and whether use of ibuprofen interfered with protective effects of aspirin. 4975 cases of acute MI and death from CHD and 20 000 controls were identified between 1997 and 2000 in the UK. The adjusted OR for any current NSAID use compared with nonuse was 1.07 (95% CI, 0.95 to 1.20). individual NSAIDs were all comparable, with

no major effect on the risk of acute MI. Naproxen was associated with an OR of 0.89 (95% CI, 0.64 to 1.24). The authors concluded there was no detectable risk reduction of NSAIDs on the occurrence of MI.

Garcia-Rodriguez LA, Varas-Lorenzo C, Maguire A, Gonzalez-Perez A. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. *Circulation* 2004; 109:3000-3006.

Mar 2004 A population-based analysis by **Whelton et al** is presented at the American College of Cardiology meeting. Objective was to determine the risk of acute myocardial infarction (AMI) or stroke with Vioxx, celecoxib, and non-selective NSAIDs in hypertensive patients. Study concludes Vioxx significantly increases the risk of AMI or stroke compared with non-users of NSAIDs and there was no increased risk among users of celecoxib or non-selective NSAIDs. Analysis evaluated 3,723 users against 1,798 users from a private medical insurance healthcare claims database. Study sponsored by Pfizer.

Whelton A, Spalding WM, White WB, Reeves MJ, Suh SS, Fort JG. Rofecoxib increases cardiovascular events in arthritis patients but celecoxib and nonspecific nonsteroidal anti-inflammatory drugs do not: results from a large New England Health Care claims database. *J Am College Cardiol* 2004; 43 (5 Suppl 2): 415A

Mar 2004 A case-control study with cases of first, nonfatal MI identified prospectively and controls identified randomly from the community, by Kimmel et al is published in the *Journal of the American College of Cardiology*. Objective was to determine the risk of nonfatal heart attacks in users of non-selective, non-aspirin NSAIDs and the interaction between non-aspirin NSAIDs and aspirin. Study concludes that in the absence of aspirin use, non aspirin NSAIDs are associated with reduced odds of MI. In those using aspirin, non aspirin NSAIDs do not provide additional protection. Analysis evaluated 581 events from the Philadelphia community among 4,153 control subjects.

Kimmel SE, Berlin JA, Muredach R, Jaskowiak J, Kishel L, Chittams J, Strom BL. The effects of nonselective non-aspirin non-steroidal anti-inflammatory medications on the risk of nonfatal myocardial infarction and their interaction with aspirin. *J Am Col Card* 2004; 43(6):985-90.

Note: There are two different analyses using the same data set. This paper (*JACC* 2004) above is different focus from the abstract in 2003. A paper based on the earlier abstract had been rejected from *Circulation*, *JAMA* and *Annals*, and now resubmitted to *Annals* at the Journal's request.

Apr 2004 A case-control study by **Solomon et al** is published in *Circulation*. Objective was to assess the risk of acute myocardial infarction (AMI) among users of Vioxx, celecoxib, and NSAIDs in an elderly population. Study concludes Vioxx all doses combined was associated with a significant increased risk of AMI compared to celecoxib. Non-significant differences were found comparing Vioxx to ibuprofen, naproxen, other NSAIDs and to those not taking NSAIDs. The risk was higher in persons taking greater than 25 mg of Vioxx and during the first 90 days of use but not thereafter. Analysis

evaluated 10,895 cases from two state-sponsored pharmaceutical benefits program in the U.S. among 54,475 patients 65 years and older. This study was first presented at the American College of Rheumatology meeting in 2003. Study sponsored by Merck.

“In all comparisons related to dose, use of rofecoxib >25 mg/d was associated with a higher adjusted relative risk of AMI than rofecoxib ≤ 25 mg. The adjusted relative risk of rofecoxib >25 mg (OR, 1.70; 95% CI, 1.07 to 2.71) was higher than that seen for ≤ 25 mg (OR, 1.21; 95% CI, 1.01 to 1.44) compared with celecoxib > 200 mg or ≤ 200 mg. The magnitude in elevation of relative risk was similar when rofecoxib was compared with no current NSAID, naproxen, ibuprofen, and other NSAIDs. Neither celecoxib dosage was associated with an elevated risk of AMI in any comparison.”

Solomon DH, Schneeweiss MD, Glynn RJ, Kiyota Y, Levin R, Mogun H. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation* 2004; 109:2068-2073.

May 2004

A population-based retrospective cohort study by **Mamdani et al** is published in *The Lancet*. Objective was to compare the rates of admission for congestive heart failure (CHF) in elderly patients who were given COX-2 inhibitors or non-selective NSAIDs. Study concludes there is a higher risk of admission for CHF in users of Vioxx and non-selective NSAIDs (diclofenac, naproxen and ibuprofen) but not celecoxib in comparison to non-users of NSAIDs. Analysis evaluated 654 events from administrative healthcare databases in Ontario among 45,097 users of NSAIDs/COX-2 inhibitors and 100,000 non users.

Mamdani M, Juurlink DN, Lee DS, Rochon PA, Kopp A, Naglie G, Austin PC, Laupacis A, Stukel TA. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart outcomes in elderly patients: a population-based cohort study. *Lancet* 2004; 363:1751-56.

Aug 2004

A case-control study by **Graham et al** is presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Objective was to determine if NSAID use increases the risk of AMI or sudden cardiac death (SCD) and if the risk is similar among COX-2 selective agents. Study concludes Vioxx use at doses greater than 25 mg increases the risk of AMI and SCD; Vioxx at 25 mg or less had an increased risk compared with celecoxib; and that several other NSAIDs increased the risk of AMI and SCD. Analysis evaluated 8,199 cases from Kaiser Permanente against a control group of 32,796 subjects. Funding provided by FDA. It is worth noting that Vioxx ≤ 25 mg was not statistically significantly different from remote NSAID use.

Table 3. Risk of AMI or SCD with current use of celecoxib, ibuprofen, naproxen, rofecoxib, or other NSAID, or recent use of a nonsteroidal agent.

NSAID USE	Cases	Controls	Adjusted OR (95% CI)
Remote use	4699	19876	1.00
Recent use	1728	6339	1.14 (1.06-1.22)
Current Use			
Celecoxib	126	497	0.86 (0.69-1.07)
Ibuprofen	674	2606	1.09 (0.99-1.21)
Naproxen	369	1416	1.18 (1.04-1.35)
Rofecoxib \leq 25 mg	58	190	1.29 (0.93-1.79)
Rofecoxib > 25 mg	10	8	3.15 (1.14-8.75)
Other NSAIDs	1864	535	1.16 (1.04-1.30)

Graham DJ, Campen D, Cheetham C, Hui R, Spence M, Ray WA. Risk of acute cardiac events among patients treated with cyclooxygenase-2 selective and non-selective nonsteroidal anti-inflammatory drugs. *Pharmacoepidemiology Drug Safety* 2004; 13:S287.

Aug 2004 A retrospective cohort study by **Rahme et al** is presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Objective was to assess the rates of hospitalizations for acute myocardial infarction (AMI) in an elderly cohort. 52,029 patients were taking non-selective NSAIDs and 71,543 patients were taking rofecoxib, with 14,056.4 and 37,371.0 person-years of exposure, respectively. Based on the regression model, the adjusted hazard ratios of hospitalizations for MI was 1.03 (0.83-1.27) for rofecoxib vs. ibuprofen/diclofenac. Study concludes there was no difference in the rate of hospitalizations for AMI among

Vioxx and the non-selective NSAIDs ibuprofen and diclofenac. Study sponsored by Merck.

Rahme E, Kong SX, Watson DJ, Toubouti Y, LeLorier J. Association between rofecoxib, diclofenac/ibuprofen and hospitalization for acute myocardial infarction. *Pharmacoepidemiology Drug Safety* 2004; 13:S235.

Aug 2004 A retrospective cohort study by **Shaya et al** is presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Objective was to examine the cardiovascular risk of COX-2 inhibitors compared to non-specific NSAIDS in a high risk Medicaid population. Analysis evaluated medical and prescription claims for Maryland Medicaid enrollees, COX-2 users numbered 1208 and non-naproxen NSAID users numbered 5274. Study concludes that COX-2 inhibitors did not increase cardiovascular risk over non-naproxen NSAIDs in a high risk population.

Shaya FT, Blume SW, Blanchette CM, Mullins CD, Weir MR. Cardiovascular risk of selective cyclooxygenase-2 inhibitors compared to other nonsteroidal anti-inflammatory agents: an observational study of a Medicaid population. *Pharmacoepidemiology Drug Safety* 2004; 13:S234.

Oct 2004 Campen presents at the American College of Rheumatology meeting the same data as was presented by Graham in Aug 2004 (see above). The abstract (below) was submitted before the analysis was complete and thus contains no results.

Results: Within an NSAID study base of 1,394,764 patients that included 40,405 exposed to celecoxib, 991,261 to ibuprofen, 435,492 to naproxen and 26,748 to rofecoxib, there were 8,199 acute cardiac events (6,675 hospitalized AMI, 1,524 sudden death). Mean age was 66.8 years and 61.8% were men. After adjustment for multiple cardiovascular risk factors, the estimated relative risk (95% confidence interval) of acute cardiac events with current use of specific NSAIDS were: celecoxib: 0.77 (0.60-0.99) p=0.04; ibuprofen: 1.13 (1.00-1.30) p=0.05; naproxen: 1.11 (0.96-1.30) p=0.17; rofecoxib = 25 mg/d: 1.02 (0.71-1.46) p=0.96; rofecoxib > 25 mg/d: 5.04 (0.94-27.06), p= 0-.06. Statistical power for this last comparison was limited by low levels of usage, with 5 exposed cases and 7 exposed controls. A telephone survey of 830 randomly selected exposed controls showed no difference between COX-2 selective, non-selective (ibuprofen, naproxen) and remote users with respect to low dose aspirin or OTC NSAID use, smoking history or family history of AMI.

Conclusion: Rofecoxib use at doses above 25 mg/d was associated with a 5-fold increased risk of AMI and sudden cardiac death. Naproxen use did not reduce risk while celecoxib use did reduce risk. This latter finding was unanticipated and may be due to chance. Additional study is needed.”

Campen DH, Graham D, Cheetham C, Shoor S, Levy G, Hui R, Spence M, Ray WA. Risk of Acute Cardiac Events Among Patients Treated with Cyclooxygenase-2 Selective and Non-selective-Nonsteroidal Anti-Inflammatory Drugs. *Arthritis & Rheumatism*, 2004; 50(9 Suppl): S657

Submitted
Oct 2004

Valentgas et al submitted a paper to JAMA describing retrospective cohort study of acute coronary events (MI or acute coronary syndrome) among 424,584 health plan enrollees ages 40-64 who used NANSAIDS by prescription from 1999-2001. Objective to estimate rates of acute coronary syndrome (ACS) in relation to use of the COX-2 inhibitor medications, rofecoxib and celecoxib, and other NANSAID drugs, naproxen, diclofenac, and ibuprofen. Compared with ibuprofen or diclofenac a combined referent group of use, the relative risk (RR) of confirmed ACS during periods of current rofecoxib use was 1.35 (95% CI 1.09-1.68). For current use of celecoxib, the RR was 1.03 (95% CI 0.83 – 1.27). There was no trend with time since onset of use, though risks in the first 30 days of rofecoxib and celecoxib were modestly elevated. There was no increased risk with higher daily doses of rofecoxib or celecoxib compared with all doses of ibuprofen or diclofenac combined. The authors concluded that the incidence of confirmed MI/ACS was greater during rofecoxib use than use of ibuprofen or diclofenac. The increased risk with rofecoxib was not clearly related to timing or dose.

The manuscript has been submitted for publication but not presented so the results are not in the public domain. The study was funded by Merck and the manuscript has Merck authors.

Valentgas P, West W, Cannuscio CC, Watson DJ, Walker AM. Cardiovascular Risk of Selective Cyclooxygenase-2 Inhibitors and Other Non-aspirin Non-steroidal Anti-inflammatory Medications. Submitted to JAMA Oct. 2004.

Nov. 2004

A paper by Juni, et al, was published in *Lancet* on November 5, 2004 after the announcement of the results of the APPROVe trial. The paper cites many but not all of the clinical trials in which VIOXX was compared to some control for efficacy and safety. From the studies cited in *Lancet*, the authors plot the relative risk of myocardial infarction vs. the cumulative patients studied and the year such data was available. Figure 2. It is noteworthy that this article compares relative risk for myocardial infarctions for VIOXX vs. a control agent. The study omitted the published data on Alzheimer's patients in which VIOXX was compared to a placebo control.

Re-analysis of by-study MI's per Juni, et al. (2004)

Background

Juni, et al. did a meta-analysis of MI relative risk (RR) for rofecoxib versus a combined comparator group including placebo, non-naproxen NSAIDs, and naproxen. Their Figure 2 shows individual study RR estimates with associated 95% confidence intervals (CI's). It is inferred from their text that (1) their individual study RR's are based on crude rates (i.e., counts of events (numerators) and numbers of patients (denominators)) rather than the typical RR's based on exposure time, (2) they added 0.5 to numerator counts for both treatments for studies in which one of the treatments had zero events to obtain finite variance for the individual study RR's, (3) they combined placebo and NSAID data for each study's RR estimate, and (4) they did not include any Alzheimer's trial data. Their Figure 2 did not identify the comparator group for each study.

Objective

Re-make Figure 2 from Juni, et al., in order to label the comparator treatment group for each individual study and add the Alzheimer's trial data (protocols 078 and 091, combined).

Data

Data are from the individual study protocols listed in Table 1. Counts of events were obtained by Maureen Kashuba from the rofecoxib CV pooled-analysis of 2003 by Saurabh Mukhopadhyay and from individual study Clinical Study Reports. Events were counted in this analysis if they were confirmed as a MI by adjudication or, for protocols not subject to adjudication, were investigator reported events that were considered MIs in the rofecoxib 2003 pooled analysis and contributed to the Antiplatelet Trialists' Collaboration (APTC) combined endpoint. Based on these definitions, there are several discrepancies between the MRL event data and that summarized by Juni, et al:

- for P029 Ext.Erich(2001), MRL data have 1 more event than Juni, et al.
- for P068 Ext.Schnitzer(1999), MRL data have 1 less event than Juni, et al.
- for P096 Truitt(2001), MRL data have 1 more event than Juni, et al.
- for P097 Ext.Geusens(2002), MRL data have 2 less events than Juni, et al.

This results in a total event count of 63 for MRL and 64 for Juni, et al. Patient years at risk (denominator) data were obtained from the rofecoxib CV pooled-analysis of 2003 by Saurabh Mukhopadhyay and from individual study CSR's as indicated in Table 1. Placebo and non-naproxen NSAID groups were combined for studies that contained both. However, 1 study (096 Truitt 2001) had both placebo and naproxen treatment groups. Data from placebo and naproxen treatment groups were not combined because of naproxen's ability to profoundly inhibit platelet function across the dosing interval and thus its potential to provide a cardioprotective benefit.

Methods

Relative risk was calculated as the rate per 100 person years for rofecoxib divided by the comparator rate per 100 person years, instead of crude rates which Juni used. This was done to account for differential discontinuation rates between treatments which we know exist in many of our studies. 0.5 was not added to numbers of events in studies with zero events in one of the treatments since the other treatment group in all such studies had only one or few events and use of 0.5 would materially alter the RR estimate. For example, assuming equal exposure in both treatment groups, if rofecoxib has 1 event and the control group has 0 events, the RR estimate is undefined or infinite. Adding 0.5 to numerator & denominator yields an RR estimate of 3.0. The 95% CI for each RR estimate was derived using the binomial distribution (with symmetric tail probabilities) of the between-treatment group split of the events, scaled for the imbalance in exposure time.

Homogeneity of hazard ratio (HR) across studies was tested using Zelen's exact test. HR and associated 95% CI was calculated for combined groups of studies according to the stratified exact conditional maximum likelihood computation of Martin and Austin (1996) using their program (<http://www.sph.emory.edu/~haustin/exactma.html>).

Results

The RR's computed via the exact binomial method (Table 1, Figure 1) are qualitatively similar to those computed by Juni, et al., except for the following:

- in cases with zero events in one treatment group, as explained in the Methods section
- 097Ext.Truitt(2001), in which the MRL RR is close to 1.0, and that of Juni, et al. is materially greater than 1.0, and

- 097Ext.Geusens(2002), in which the event count data are off by 2.

For the 2nd bullet, the ratio of exposure time is similar to that of numbers of patients, so this difference in denominator is likely not the reason for this discrepancy. It remains unknown.

All non-naproxen-controlled studies have 95% CI's which largely overlap 1.0. Thus, examination of these non-naproxen controlled individual study data, whether via calculations by Juni, et al. or MRL are consistent with similarity of MI risk between rofecoxib and non-naproxen controls. The implication in the Juni publication that data from these studies that were not adjudicated by an external panel are somehow not accurate or have been inappropriately manipulated by MRL is totally false.

Juni et al. used an imprecise test for homogeneity among the individual studies. Implementation of Zelen's Exact test for homogeneity of HR across all the studies in Figure 1 and Table 1 reveal statistically significant heterogeneity ($p=0.042$); thus, their combining of all studies is inappropriate as described in detail in Merck's response to the Juni et al. publication [http://www.merck.com/statement_2004_1105/lancet.pdf]. Grouping all non-naproxen-controlled studies yielded no statistically significant heterogeneity of HR across studies ($p=0.534$). The combined HR estimated from the non-naproxen-controlled studies was 1.16 (0.63,2.13), close to 1.0, which is similar to that found in the MRL analyses. Importantly, because the confidence interval crosses 1, the result is not statistically significant.

For the naproxen-controlled studies, the test of homogeneity was still rejected ($p=0.043$). Visual inspection of the naproxen-controlled studies RR's revealed two distinct groups, one with RR's < 1, the other with RR's > 1:

- (1) VIGOR (prot.088) + ADVANTAGE(prot.102) + the Phase III RA 12-week controlled trial (prot.096 Part I) .For this set of trials the test of homogeneity of HR was not rejected ($p>0.5$), and the HR estimate was 5.22 (95% CI 2.08, 13.12), consistent with a decreased risk associated with naproxen and the result reported by Bombardier, et al.
- (2) The Phase IIb/III RA extension trials (068Ext, 096Ext, and 097Ext). For this second set of naproxen-controlled trials, the test of homogeneity was not rejected ($p=0.484$), and the HR estimate was 0.65 (95% CI 0.20,2.12), consistent with similarity of risk between rofecoxib and naproxen.

Thus, had Juni et al. done more powerful statistical analyses to detect heterogeneity across the trials, they would have come to the same conclusions as Konstam, et al. (2002) and Weir, et al. (2003).

Figure 2 of this report displays the individual study results as displayed in Figure 1, but includes the 3 combined estimates of HR cited above.

Although this split of the naproxen studies removes the significant heterogeneity across studies, it does not explain why this heterogeneity occurs. One interpretation of the RA extension trials is that they could be representative of the same pattern of difference displayed in protocols 088, 102, and 096 Part I, but this pattern was not realized because of small numbers of events. Under this interpretation, the combined HR across all naproxen studies was 3.02 (95% CI 1.46, 6.24). Figure 3 displays this combined estimate and that of the non-naproxen-controlled studies, in addition to all the individual study results. Another interpretation is that since the extension-containing trials are a non-randomized subset of patients, i.e., those who elect to continue, they may not represent the same population which was randomized to the respective trials. Rather, the patients sensitive to the CV treatment difference observed in VIGOR may not have elected to enter these extensions. Thus, inclusion of the extension-containing studies could bias the naproxen estimate and only the 3 randomized studies should be

included to estimate the naproxen effect. Other hypotheses could also be entertained. In any event, the reason for the heterogeneity in the naproxen studies cannot be known from these analyses.

Table 2 displays the same information as Table 1, but instead it is broken by the 4 groups of studies for which combined HR estimates were provided.

References

Juni P, Nartey L, Richenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Published online November 5, 2004

<http://image.thelancet.com/extras/04art10237web.pdf>.

Martin DO and Austin H. Exact estimates for a rate ratio. *Epidemiology* 1996;7:29-33.

Zelen M. The analysis of several 2 x 2 contingency tables. *Biometrika* 1971;58:129-137.

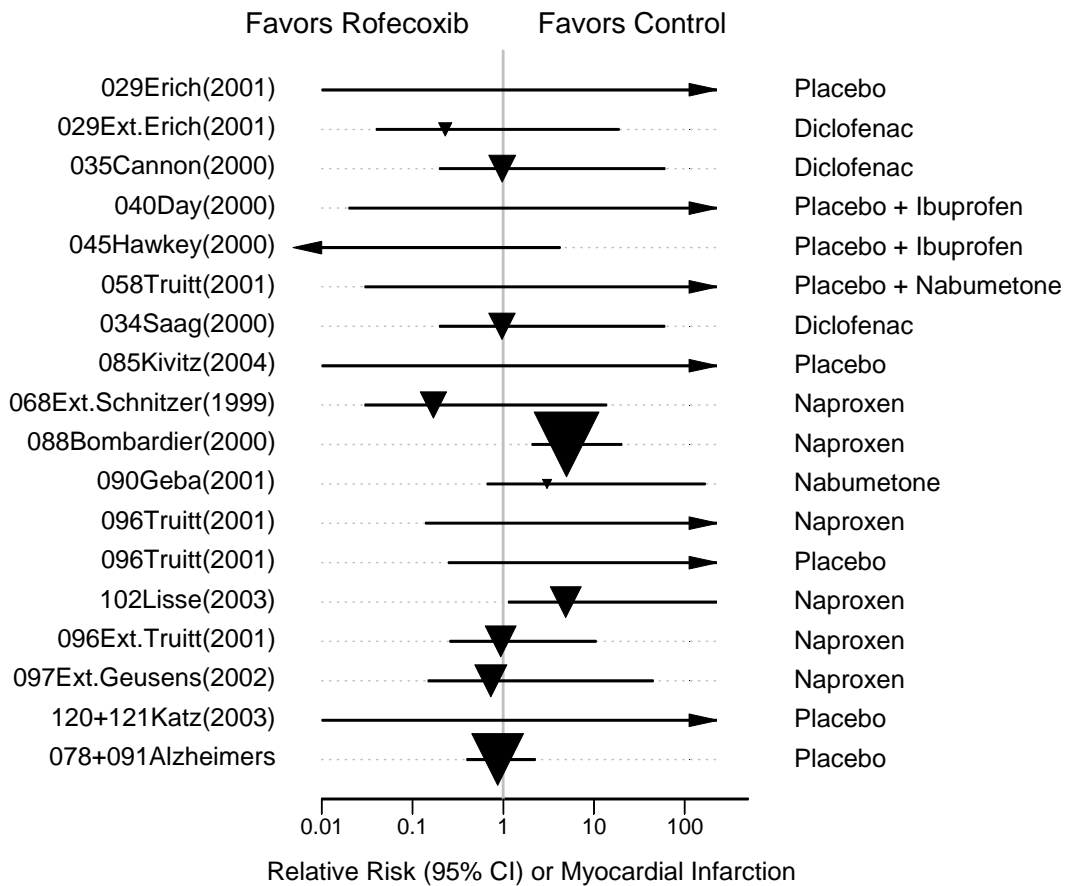
Table 1 – MI's, Exposure, and RR's for studies in Juni, et al. (2004)

study	rofe #events	rofe pat. yrs	control #events	control pat. yrs	relative risk	lower 95%CL	upper 95%CL	control
a: 029Eri ch(2001)	1	46	0	16	.*	0.01	.*	pl acebo
b: 029Ext. Ehri ch(2001)	1	196 a	1	45 a	0.23	0.04	18.90	di cl ofenac
c: 035Cannon(2000)	2	645	1	315	0.98	0.20	60.56	di cl ofenac
d: 040Day(2000)	1	72	0	48	.	0.02	.	pl acebo+i buprofen
e: 045Hawkey(2000)	0	157	2	125	0.00	0.00	4.24	pl acebo+i buprofen
f: 058Trui tt(2001)	1	21	0	23 b	.	0.03	.	pl acebo+nabumetone
g: 034Saag(2000)	2	635	1	309	0.97	0.20	60.34	di cl ofenac
h: 085Ki vi tz(2004)	1	61	0	28	.	0.01	.	pl acebo
i: 068Ext. Schni tzer(1999)	1	788	1	132	0.17	0.03	13.79	naproxen
j: 088Bombardi er(2000)	20	2807	4	2809	5.00	2.09	20.29	naproxen
k: 090Geba(2001)	3	56	1	57	3.05	0.67	168.63	nabumetone
l: 096Trui tt(2001)	3	97	0	34 c	.	0.14	.	naproxen
m: 096Trui tt(2001)	3	97	0	58	.	0.25	.	pl acebo
n: 102Li sse(2003)	5	640	1	629	4.91	1.15	244.72	naproxen
o: 096Ext. Trui tt(2001)	4	864 d	2	408 d	0.94	0.26	10.51	naproxen
p: 097Ext. Geusens(2002)	2	995	1	361	0.73	0.15	44.99	naproxen
q: 120+121Katz(2003)	1	51	0	25	.	0.01	.	pl acebo
r: 078+091Al zheimers	9	1661	12	1930	0.87	0.40	2.26	pl acebo
s: non-naproxen combin ed	25	2561	18	2979	1.16	0.63	2.13	non-naproxen
t: naproxen combin ed	35	6191	9	4373	3.02	1.46	6.24	naproxen
u: 088+102+096Trui tt(2001)	28	3544	5	3472	5.22	2.08	13.12	naproxen
v: 068+096+097 Ext.	7	2647	4	901	0.65	0.20	2.12	naproxen

NOTES:

- Pat.yrs extracted from 2003 CV meta-analysis report, except as indicated by a, b, c, d:
 - a- from the 029-10 CSR
 - b- from the 058 base study CSR
 - c- from the 096 base study CSR
 - d- from the 096 Part II and Extension CSR's
- dots (`. `) indicate that the value is undefined (infinite); for these cases the confidence limit is one-sided, 97.5% for consistency with each tail of the two-sided 95% CI's
- for 045Hawkey(2000) the Relative Risk estimate is 0 and the confidence limit is one-sided 97.5% for consistency with each tail of the two-sided 95% CI's

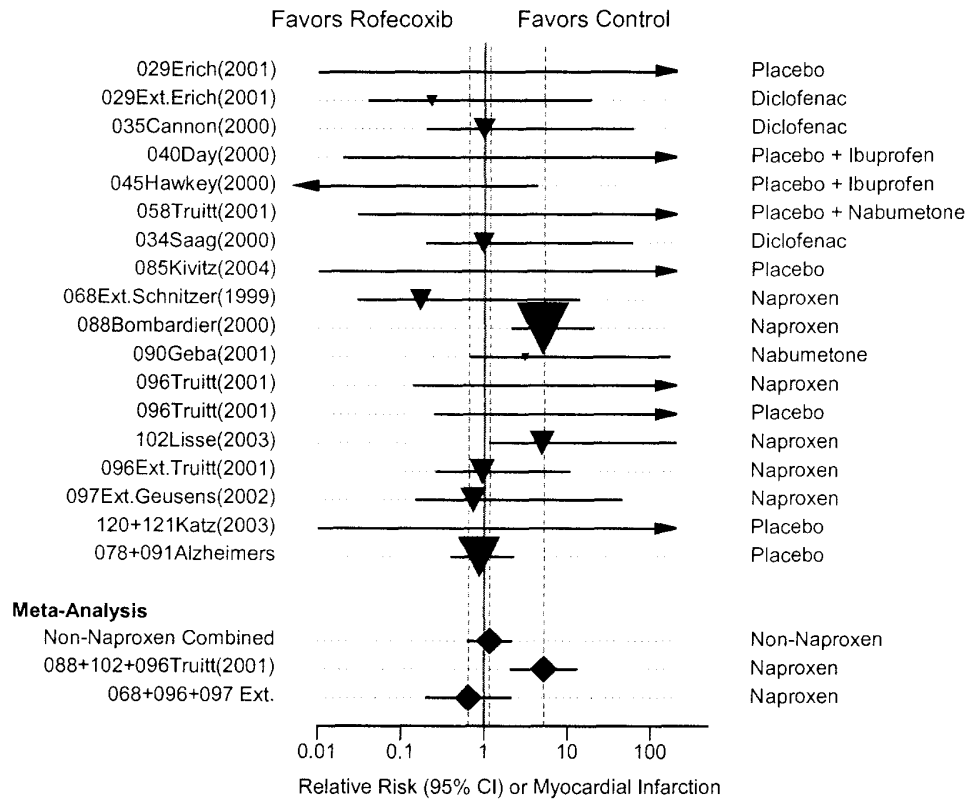
Figure 1 – Relative Risk and 95% Confidence Intervals for MI from individual studies in Juni, et al. (2004)



NOTES:

- x-axis is on log scale
- size of point estimates (triangles) is proportional to total treatment exposure. It is worth noting the size of the triangle in 090 which shows the lowest patient exposure of any trial. This study has been singled out in press reports as the study which should have indicated that Vioxx caused cardiovascular risk. Studies such as 035, 034, 029 or 045 have never been cited by MRL to claim cardioprotection by Vioxx.
- left-pointing arrow indicates 0 events on rofecoxib; thus, point estimate is 0, lower confidence limit is not defined, and upper confidence limit is one-sided 97.5% in order to be consistent with two-sided 95% CI's for studies with finite confidence limits
- right pointing arrows indicate 0 events on comparator; thus, point estimate is undefined (infinite), upper confidence limit is not defined, and lower confidence limit is one-sided 97.5% in order to be consistent with two-sided 95% CI's for studies with finite confidence limits

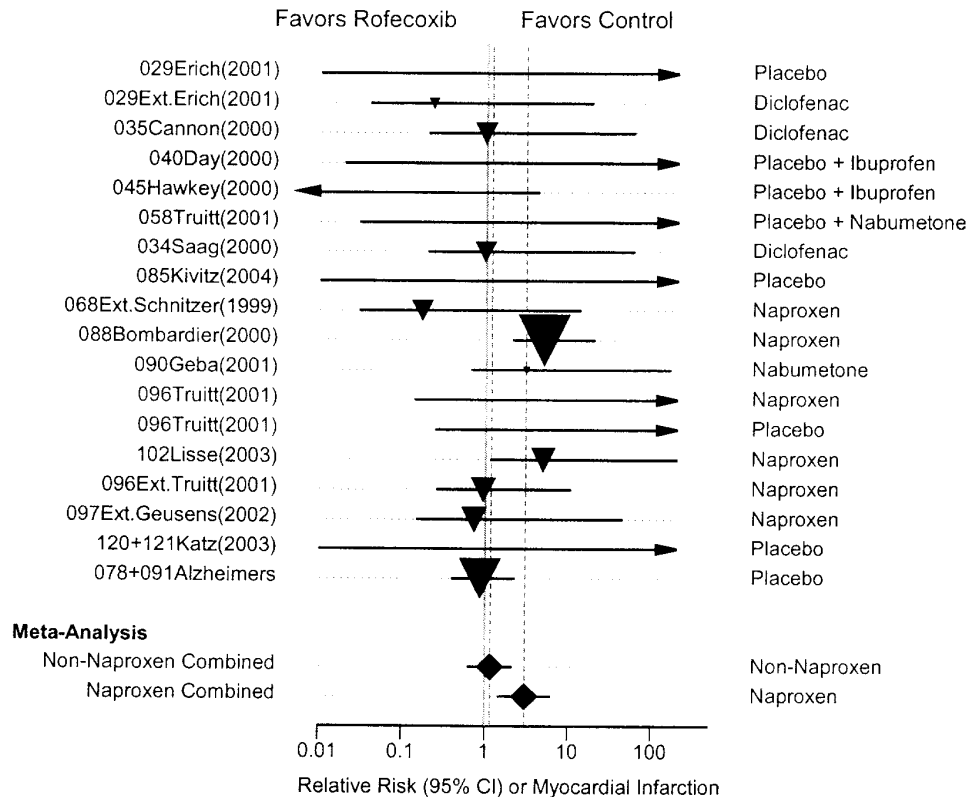
Figure 2 – RR and 95% CI's for MI from individual studies in Juni, et al. (2004) plus 3 combined-studies estimates



NOTES:

- x-axis is on log scale
- size of point estimates (triangles) is proportional to total treatment exposure
- left-pointing arrow indicates 0 events on rofecoxib; thus, point estimate is 0, lower confidence limit is not defined, and upper confidence limit is one-sided 97.5% in order to be consistent with two-sided 95% CI's for studies with finite confidence limits
- right pointing arrows indicate 0 events on comparator; thus, point estimate is undefined (infinite), upper confidence limit is not defined, and lower confidence limit is one-sided 97.5% in order to be consistent with two-sided 95% CI's for studies with finite confidence limits

Figure 3 – RR and 95% CI's for MI from individual studies in Juni, et al. (2004) plus 2 combined-studies estimates (all non-naproxen-controlled studies combined and all naproxen-controlled studies combined)



NOTES:

- x-axis is on log scale
- size of point estimates (triangles) is proportional to total treatment exposure
- left-pointing arrow indicates 0 events on rofecoxib; thus, point estimate is 0, lower confidence limit is not defined, and upper confidence limit is one-sided 97.5% in order to be consistent with two-sided 95% CI's for studies with finite confidence limits

right pointing arrows indicate 0 events on comparator; thus, point estimate is undefined (infinite), upper confidence limit is not defined, and lower confidence limit is one-sided 97.5% in order to be consistent with two-sided 95% CI's for studies with finite confidence limits

Table 2 – MI's, Exposure, and RR's for studies in Juni, et al. (2004), split by comparator group

study	rofe #events	rofe pat. yrs	control #events	control pat. yrs	relative risk	lower 95%CL	upper 95%CL
control							
non-naproxen controlled studies							
a: 029Erich(2001) placebo	1	46	0	16	. *	0. 01	. *
b: 029Ext. Ehrich(2001) diclofenac	1	196 a	1	45 a	0. 23	0. 04	18. 90
c: 035Cannon(2000) diclofenac	2	645	1	315	0. 98	0. 20	60. 56
d: 040Day(2000) placebo+bupropion	1	72	0	48	.	0. 02	.
e: 045Hawkey(2000) placebo+bupropion	0	157	2	125	0. 00	0. 00	4. 24
f: 058Truitt(2001) placebo+nabumetone	1	21	0	23 b	.	0. 03	.
g: 034Saag(2000) diclofenac	2	635	1	309	0. 97	0. 20	60. 34
h: 085Kivitz(2004) placebo	1	61	0	28	.	0. 01	.
k: 090Geba(2001) nabumetone	3	56	1	57	3. 05	0. 67	168. 63
m: 096Truitt(2001) placebo	3	97	0	58	.	0. 25	.
q: 120+121Katz(2003) placebo	1	51	0	25	.	0. 01	.
r: 078+091Alzheimers placebo	9	1661	12	1930	0. 87	0. 40	2. 26
s: non-naproxen combined non-naproxen	25	2561	18	2979	1. 16	0. 63	2. 13
naproxen-controlled studies							
i: 068Ext. Schnitzer(1999) naproxen	1	788	1	132	0. 17	0. 03	13. 79
j: 088Bombardier(2000) naproxen	20	2807	4	2809	5. 00	2. 09	20. 29
l: 096Truitt(2001) naproxen	3	97	0	34 c	.	0. 14	.
n: 102Lisse(2003) naproxen	5	640	1	629	4. 91	1. 15	244. 72
o: 096Ext. Truitt(2001) naproxen	4	864 d	2	408 d	0. 94	0. 26	10. 51
p: 097Ext. Geusens(2002) naproxen	2	995	1	361	0. 73	0. 15	44. 99
t: naproxen combined naproxen	35	6191	9	4373	3. 02	1. 46	6. 24

Table 2 (cont.) – MI's, Exposure, and RR's for studies in Juni, et al. (2004), split by comparator group

study	rofe #events	rofe pat.yrs	control #events	control pat.yrs	relative risk	lower 95%CL	upper 95%CL
control							
Group (1) of naproxen-controlled studies							
j: 088Bombardier(2000) naproxen	20	2807	4	2809	5.00	2.09	20.29
l: 096Truitt(2001) naproxen	3	97	0	34 c	.	0.14	.
n: 102Lisse(2003) naproxen	5	640	1	629	4.91	1.15	244.72
u: 088+102+096Truitt(2001) naproxen	28	3544	5	3472	5.22	2.08	13.12
Group (2) of naproxen-controlled studies							
i: 068Ext. Schnitzer(1999) naproxen	1	788	1	132	0.17	0.03	13.79
o: 096Ext. Truitt(2001) naproxen	4	864 d	2	408 d	0.94	0.26	10.51
p: 097Ext. Geusens(2002) naproxen	2	995	1	361	0.73	0.15	44.99
v: 068+096+097 Ext. naproxen	7	2647	4	901	0.65	0.20	2.12

The statistical analyses that have been performed on this section of the document were performed by James Bolognese of MRL in consultation with Dr. Scott Zeger, Chairman of the Department of Biostatistics at Johns Hopkins University.

Summary:

Nine retrospective analyses of NSAID and VIOXX use performed after March 2000 until October 2004 in over 500,000 patients did not detect enhanced cardiovascular event rates in patients using Rofecoxib at dosages indicated for chronic use, 12.5 mg or 25 mg compared to other traditional NSAIDs. Some studies showed risk reduction for users of naproxen and some did not. It is difficult to determine the degree of rigorous compliance to daily twice a day dosing of naproxen at 500 mg doses in such studies. Since naproxen is not an irreversible inhibitor of platelet COX-1 (as noted above) vigorous full compliance would be necessary to expect a cardioprotective effect.

It is also noteworthy that the article in *Lancet*, November 2004, compares relative risk for myocardial infarctions of VIOXX vs. a control agent. The study omitted the published Alzheimer's patients where VIOXX was compared to a placebo control. As noted in Figure recalculated by MRL, the increased relative risk of MI for VIOXX vs. control is due to the

studies in which VIOXX was compared to naproxen as noted previously by MRL scientists. Although it is possible to deduce this from the article as originally published in *Lancet*, it is not easy to do so. The new figure included above shows this conclusion more clearly. A letter written by the Swedish Regulatory Agency draws the same conclusion: “[T]here was before the APPROVe trial no controlled data which indicated that rofecoxib would be different from placebo with regard to the risk for myocardial infarction and there was no basis to at an earlier time point withdraw VIOXX from the market.” MRL did not solicit the letter.

Retrospective Studies of 50 mg dose and VIOXX label

The Ray article, *Lancet*, 360, 1071-1073, 2002, the Solomon article, *Circulation*, May 4, 2002, 2068-2073, the Campen abstract in *Arthritis and Rheumatism*, Aug and Oct 2004, and the Graham analysis, August 2004, Table 3, all point out an elevated risk of cv events at dosages >25mg/day, above the maximum indicated dosage of 12.5-25 mg for chronic use. Merck’s label indicating proper dosage of VIOXX in 2000 and 2002 is noted below. Also noted is the effect of 50 mg on blood pressure, salt and water retention in the label.

2000 Label

PRECAUTIONS

* * *

Renal Effects

Clinical trials with VIOXX at daily doses of 12.5 and 25 mg have shown renal effects(e.g., hypertension, edema) similar to those observed with comparator NSAIDs; these occurred with an increased frequency with chronic use of doses above the 12.5 to 25 mg range. (see ADVERSE REACTIONS)

* * *

Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking VIOXX (see ADVERSE REACTIONS). VIOXX should be used with caution, and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or heart failure.

* * *

DOSAGE AND ADMINISTRATION

Osteoarthritis

The recommended starting dose of VIOXX is 12.5 mg once daily. Some patients receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

Management of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended dose of VIOXX is 50 mg once daily. Subsequent doses should be 50 mg once daily as needed. Use of Vioxx for more than 5 days is management of pain has not been studied.

April 2002 Label

PRECAUTIONS

* * *

Fluid Retention, Edema, and Hypertension

Fluid retention, edema, and hypertension have been reported in some patients taking VIOXX. In clinical trials of VIOXX at daily doses of 25 mg in patients with rheumatoid arthritis the incidence of hypertension was twice as high in patients treated with VIOXX as compared to patients treated with naproxen 1000 mg daily. Clinical trials with VIOXX at daily doses of 12.5 and 25 mg in patients with osteoarthritis have shown effects on hypertension and edema similar to those observed with comparator NSAIDs; these occurred with an increased frequency with chronic use of VIOXX at daily doses of 50 mg. (See ADVERSE REACTIONS.) VIOXX should be used with caution, and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or heart failure.

DOSAGE AND ADMINISTRATION

Osteoarthritis

The recommended starting dose of VIOXX is 12.5 mg once daily. Some patients receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

Rheumatoid Arthritis

The recommended dose is 25 mg once daily. The maximum recommended daily dose is 25 mg.

Management of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended dose of VIOXX is 50 mg once daily. The maximum recommended daily dose is 50 mg. Use of Vioxx for more than 5 days is

management of pain has not been studied. Chronic use of VIOXX 50 mg daily is not recommended. (See ADVERSE Reactions, Clinical Studies in OA and RA with VIOXX 50 mg).

As noted above, two articles in 2002 and two articles in 2004 noted increased CV or congestive heart failure risk associated with chronic use of doses of VIOXX greater than 25 mg. Presumably this involved use of 50 mg or possibly even higher doses. The FDA approved label for VIOXX has clearly stated that the maximum indicated dose for chronic use was 25 mg and that the starting dose was 12.5 mg per day. The label has disclosed that use of 50 mg for times longer than five days (acute pain indication) in controlled clinical trials was associated with increased incidence of fluid retention, edema, and increased blood pressure as noted above.

The APPROVe Trial

APPROVe was a multi-center, randomized, placebo-controlled, double-blind study to determine the effect of 156 weeks (3 years) of treatment with rofecoxib on the recurrence of adenomatous polyps of the large bowel in patients with a history of colorectal adenomas. The study included approximately 2586 patients aged 40-96; approximately 62% male. Aspirin was allowed in the study.

No difference in results from the APPROVe trial was detectable for the first 18 months of continuous use of VIOXX 25 mg in the trial with regard to risk of cardiovascular thrombotic events. It was only after a much longer period of consecutive months of VIOXX 25 mg versus placebo that the risk for cardiovascular thrombotic events was elevated in the VIOXX arm, slightly less than twofold. The cardiovascular event rate began to diverge between the VIOXX and placebo arms after 18 months of continuous treatment, and the data finally became statistically significant after this much longer period of months. The event rate diverged similarly in patients taking low-dose ASA and in patients not taking ASA. It is important to emphasize that the ESMB (External Safety Monitoring Board) that followed the results had totally independent authority to halt the trial at any point. They chose to stop the trial when the results first became statistically significant. It is also important to emphasize that the fact that the CV event rate did not begin to diverge from the placebo arm until after 18 months is

consistent with the earlier Alzheimer's data and our conclusions from the VIGOR study (which lasted only approximately one year) that VIOXX was not prothrombotic. The meaning of the APPROVe data is also confounded by the fact that the CV event rate in the placebo arm turns relatively flat after 18 months, an unusual and unexplained course, which indicates very few CV events in the placebo arm after 18 months. Thus, it is not clear to me from the data available to me what the explanation is for the divergence in curves after 18 months.

References:

Bombardier C., Laine L., Reicin A., Shapiro D., Burgos-Vargas R., David B., et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; 343:1520-1528.

ⁱ Konstam M., Weir M., Reicin A., Shapiro D., et al. Cardiovascular Thrombotic Events in Controlled, Clinical Trials of Rofecoxib. *Circulation* 2001; 104:1-9.

ⁱⁱ Brochier ML. Evaluation of flurbiprofen for prevention of reinfarction and reocclusion after successful thrombolysis or angioplasty in acute myocardial infarction. *Eur Heart J* 1993:951-7.