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Joan Claybrook, President

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Dr. Lester M. Crawford, Acting Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

**CITIZEN'S PETITION TO REMOVE THE COX-2 INHIBITORS CELECOXIB
(CELEBREX) AND VALDECOXIB (BEXTRA) FROM THE MARKET**

Dear Dr. Crawford:

Public Citizen, a nationwide consumer organization with a membership of more than 150,000, hereby petitions the Food and Drug Administration (FDA) pursuant to the Federal Food, Drug, and Cosmetic Act 21 U.S.C. Section 355 (e) (3), and 21 C.F.R. 10.30 to immediately remove the COX-2 inhibitors celecoxib (Celebrex) and valdecoxib (Bextra) from the market because of their cardiovascular risks. In 2004, a total of more than 36 million prescriptions were filled in the U.S. for these drugs (23.9 million for Celebrex and 12.9 million for Bextra—IMS data).

The COX enzymes synthesize signaling molecules called prostaglandins in various tissues. COX-1 is expressed all the time (constitutively) in many tissues, such as the gastric mucosa where it protects against the formation of ulcers. COX-2 was initially discovered because it was produced by tissues in inflammatory states. COX-2 selective inhibitors were created to block the inflammatory signals generated by COX-2 without causing the adverse effects resulting from COX-1 inhibition, specifically ulcers and their complications of bleeding, obstruction, or perforation.

Evaluating a drug involves computing the risk to benefit ratio it provides patients. If a drug offers no unique benefit compared to other drugs for treating the same problem (in this case arthritis and pain) but subjects patients to a unique risk, it must be removed from the market. Despite the claims for this class of drugs, neither celecoxib nor valdecoxib has demonstrated a reduction in clinically significant upper gastrointestinal (GI) events compared to older non-steroidal anti-inflammatory drugs (NSAIDs). Neither drug has proved that it has any greater efficacy than other non-selective NSAIDs. Instead, there is mounting evidence of cardiac toxicity with these drugs similar to that seen with Vioxx and which resulted in Vioxx's removal from the market in September of 2004. Published and unpublished studies for two other COX-2 inhibitors which are not approved by the FDA, lumiracoxib and etoricoxib, also provide evidence of increased cardiovascular risk for all COX-2 inhibitors. A

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proposed mechanism for the increased thrombogenicity (the tendency for blood clots to form, as in a heart attack) of these drugs has been investigated and points to a class effect of COX-2 inhibitors. In this petition, we will examine the results from 14 randomized control trials involving the five drugs in this class and show that most of the studies demonstrate a rise in cardiovascular toxicity due to a COX-2 class effect. This petition is also based on a review of other published and unpublished scientific information on the COX-2 enzyme and COX-2 inhibitors.

Increased Thrombotic Cardiovascular Risk Seen in COX-2 Inhibitors Randomized, Controlled Clinical Trials

Rofecoxib (Vioxx)

Rofecoxib was voluntarily removed from the market in September 2004 by the manufacturer, Merck, due to the increased rate of myocardial infarctions seen in the APPROVe trial, which was stopped prematurely for these safety reasons. The APPROVe trial was a 3 year study involving 2600 patients that investigated the efficacy of rofecoxib for prevention of colon polyps when compared to placebo. After 18 or more months of treatment, patients taking rofecoxib had twice the risk of a myocardial infarction compared with those receiving placebo (3.5% vs. 1.9%).^{1,2} The relative risk for a thrombotic event seen with Vioxx was 1.96 (p=0.007), and “was similar in both high and low (CV) risk patients” according to Merck officials.³

This information supports the previous results of the VIGOR trial which followed 8076 patients over 9 months to measure the risk of GI toxicity compared to naproxen and was published in November 2000. It showed a statistically significant four-fold increase in the risk of having a myocardial infarction in patients taking rofecoxib (0.4%) compared with those taking naproxen (0.1%).⁴ The relative risk for all serious thrombotic cardiovascular adverse events (encompassing myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke, and transient ischemic attack) was 2.38 for the rofecoxib treatment group (95% CI 1.39-4.00). The relative risk of this outcome jumped to 4.89 (95% CI 1.41-16.88) in those patients in the trial for whom low-dose aspirin was indicated because of a previous cardiovascular history but who were not presently taking aspirin.⁵

A review completed in 2001 took the VIGOR study data set and the unpublished full CLASS study data set (for celecoxib—Celebrex) and compared them to the placebo group from a meta-analysis of other studies evaluating the primary prevention of myocardial

¹ FDA News. FDA issues public health advisory on Vioxx as its manufacturer voluntarily withdraws the product. Sept 30, 2004. (Accessed Jan 4, 2005 at www.fda.gov/bbs/topics/news/2004/NEW01122.html)

² News Interactive. Arthritis drug ‘a killer’. Dec 18, 2004. (Accessed Jan 5, 2005 at www.news.com.au/common/story_page/0,4057,11720748%255E3102,00.html)

³ Peterson, L. The cardiovascular safety of COX-2 inhibitors. Trends-in-Medicine Nov 2004.

⁴ Bombardier C, Laine L, Reicin A et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000; 343:1520-8.

⁵ Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001; 286:954-9.

infarction with low-dose aspirin. This analysis revealed a higher annualized myocardial infarction rate for rofecoxib in the VIGOR trial than in the aspirin meta-analysis placebo group. (Placebo 0.52%; VIGOR 0.74%, P=0.04)⁵

Celecoxib (Celebrex)

The CLASS study published in 2000 assessed the incidence of clinically significant upper GI events seen over 1 year of treatment with celecoxib compared to ibuprofen and diclofenac. The authors combined the ibuprofen and diclofenac arms into one active comparator group for the overall study, but they also analyzed the two substudies separately. A post hoc analysis was done between those patients taking low-dose aspirin for cardiac protection and those patients not taking low-dose aspirin. The published article found that the incidence of cerebrovascular accident, myocardial infarction, and angina was not statistically different between patients taking the three drugs.⁶ However, the published data only reflected a 6-month period used by the company to espouse an unsupportable claim of decreased GI toxicity. We chose to focus on the complete 12 months of data from the CLASS study available from the FDA reviews on celecoxib.

This 12-month data set revealed that the rate of combined anginal adverse events was 1.4% in the celecoxib group versus 1.0% in either NSAID group, a non-statistically significant difference.⁷ This tendency toward increased cardiovascular toxicity was described by FDA Medical Officer Dr. Witter, "For anginal disorders (especially the combined disorders), there seems to be a trend toward more [cardiac adverse] events in those patients receiving celecoxib, regardless of aspirin use."⁸

This trend was magnified in those patients not taking low-dose aspirin. Combined anginal disorders were increased in these patients; the celecoxib group had 0.6% vs. 0.2% and 0% in the diclofenac and ibuprofen groups, respectively. There were also more combined atrial serious cardiac adverse events with celecoxib, 0.3% compared to 0.1% and 0% in the diclofenac and ibuprofen groups, respectively. Dr. Witter commented, "In the non-aspirin users, there appears to be a slight trend toward more [serious cardiac adverse] events in those patients receiving celecoxib for combined atrial and anginal disorders". Additionally, the rate of myocardial infarction was higher in the celecoxib group, 0.2%, compared with the other two drugs, 0.1%. Dr. Witter also referred to data from the original NDA for celecoxib in his discussion, "There were suggestions of a dose-response relationship (... 100mg BID celecoxib, 0% crude mortality rate vs. 400 mg BID celecoxib, 0.64% crude mortality rate) between cardiovascular mortality and [increased] celecoxib use that could not be adequately addressed by the data."⁸

⁶ Silverstein FE, Faich G, Goldstein JL et al. Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. JAMA 2000; 284:1247-55.

⁷ Throckmorton DC. Comparative safety of celecoxib, diclofenac, and ibuprofen. Food and Drug Administration Memorandum January 5, 2001.

⁸ Witter J. Celebrex capsules (celecoxib). Food and Drug Administration Medical Officer Review June 12, 2000; NDA 20-998/S-009.

The FDA was concerned enough that they ordered a cardiorenal consult by Medical Officer Dr. Throckmorton on the same CLASS study data. In his report he noted, "The CLASS trial data do not support a large adverse effect of celecoxib on cardiovascular mortality or on serious adverse events related to thrombosis relative to either diclofenac or ibuprofen. The data do not exclude a less apparent pro-thrombotic effect of celecoxib, such as might be reflected in the relative rates of cardiac adverse events related to ischemia."⁷

While none of the CLASS data was statistically significant, they revealed a consistent and worrisome trend toward increased cardiovascular toxicity, particularly that related to increased thrombosis. Celecoxib is the least selective of the COX-2 inhibitors. This could explain why, unlike rofecoxib, it did not show a decrease in clinically significant upper GI events compared to the other NSAIDs (ibuprofen and diclofenac) and why in the CLASS study it had a lesser cardiovascular signal than rofecoxib did in the VIGOR study. However, this cardiovascular signal seen in a limited number of patients exposed for a relatively short period of time should not have been ignored because of the implications for the millions of patients using celecoxib on a long-term basis.

The review mentioned previously did find that the annualized myocardial infarction rate was statistically significantly higher in the CLASS trial compared to the placebo group from a meta-analysis of other studies evaluating the primary prevention of myocardial infarction with low-dose aspirin. (Placebo 0.52%; CLASS 0.80%, P=0.02) To explain why this was not statistically significantly different from the active comparators in the trial, unlike rofecoxib in VIGOR, the authors theorized, "Diclofenac causes 94% inhibition of COX-2 compared with 71% inhibition of COX-2 for naproxen. Thus, diclofenac not only has less antiplatelet effect, but may have some intrinsic pro-thrombotic effect among NSAIDs due to inhibition of vasodilatory PGI₂ and this may have masked the increase in event rates with celecoxib." Their recommendations were, "Our findings suggest a potential increase in cardiovascular event rates for the presently available COX-2 inhibitors...definitive evidence of such an adverse effect will require a prospective randomized clinical trial...Given the remarkable exposure and popularity of this new class of medications, we believe that it is mandatory to conduct a trial specifically assessing cardiovascular risk and benefit of these agents. Until then, we urge caution in prescribing these agents to patients at risk for cardiovascular morbidity."⁵ Although employing a placebo group from a different trial weakens the validity of their analysis, the author's call for a prospective randomized clinical trial powered to truly analyze the cardiovascular risk to benefit ratio was then exactly correct. Recently, however, such a placebo-controlled trial of celecoxib has clearly demonstrated this risk.

This trial was the APC colon polyp recurrence prevention study, in which approximately 2000 patients took celecoxib or placebo. Interestingly, this was the longest celecoxib trial to date with mean duration of treatment being 33 months as opposed to the much shorter 12-month duration of the CLASS study. A statistically significant elevation in the risk for a major fatal or non-fatal cardiovascular event (a composite endpoint of cardiovascular death, acute myocardial infarction, and stroke) was seen in those patients taking celecoxib compared to those in the placebo group. This followed a dose-response relationship: the relative risk at

400mg/day of celecoxib was 2.5 while the relative risk at 800mg/day was 3.4.^{9,10} Because of this unacceptable danger, the trial was prematurely halted. The FDA released an explanatory statement which said, "While we have not seen all available data on Celebrex, these findings are similar to recent results from a study of Vioxx (rofecoxib), another drug in the same class as Celebrex. Vioxx was recently voluntarily withdrawn by Merck."¹¹

Data monitoring committees reviewed the safety data for two other large, long-term prevention studies, PreSAP for colon polyps and ADAPT for Alzheimer's disease, at the same time but have not yet discovered a statistically significant change in the cardiovascular risk; so the studies were allowed to continue⁹. Neither of these studies has been published, so we are relying on fragmentary and preliminary information derived from news articles. Therefore, a trend towards increased cardiovascular risk in these two studies that has not yet reached statistical significance could well be present. ADAPT was later halted because patients were so concerned by the NIH announcement regarding the increased CV risk seen in the APC trial that it caused some elderly patients to stop taking their pills, fearing they might be taking Celebrex instead of naproxen or a placebo, according to Susan Molchan, the director of the Alzheimer's disease clinical trials program at the NIH's National Institute on Aging.¹² ADAPT was not stopped because of a small, statistically insignificant, increase in heart attacks observed in the naproxen arm.

Valdecoxib (Bextra)

Parecoxib is an intravenous COX-2 inhibitor which the body rapidly metabolizes to the active form, valdecoxib. It was used in the post-surgical clinical trials before the patients could eat or drink, after which they were converted to valdecoxib pills. However, the FDA rejected parecoxib when it came up for approval.

The package labeling for valdecoxib contains the results of two trials following coronary artery bypass grafting (CABG). The first trial was published by Ott et al and also appears to be included in the FDA review of valdecoxib, although we are not confident of this because of conflicting data. In this group of especially high-cardiovascular risk patients, death and serious adverse events (myocardial infarction, cerebrovascular accident, deep venous thrombosis, pulmonary embolism, congestive heart failure, renal dysfunction or failure as well as non-cardiorenal adverse events) were significantly increased in the parecoxib/valdecoxib group, 25.7% vs. 15.2% in the placebo group (p=0.012). Specifically, the rate of myocardial infarction (MI) in the parecoxib/valdecoxib group, 2.6%, was twice that seen in the placebo group, 1.3%. FDA Medical Officer Dr. Johnson remarked in his review, "The excess of serious cardiovascular thromboembolic events in the valdecoxib arm

⁹ FDA Alert for Practitioners. Celebrex (celecoxib). Dec 17, 2004. (Accessed Jan 4, 2005 at www.fda.gov/cder/drug/infopage/celebrex/celebrex-hcp.pdf)

¹⁰ Pfizer Inc. News Release. Pfizer statement on new information regarding cardiovascular safety of Celebrex. Dec 17, 2004. (Accessed Jan 4, 2005 at www.celebrex.com/cardiovascular_safety_of_celebrex_tp.asp)

¹¹ FDA. FDA statement on the halting of a clinical trial of the Cox-2 inhibitor Celebrex. Dec 17, 2004 (Accessed Jan 4, 2005 at www.fda.gov/bbs/topics/news/2004/new01144.html)

¹² Ragalado A and Winslow R. Some scientists say Aleve's dangers may be overblown. The Wall Street Journal Dec 23, 2004: page B1.

of the CABG trial...is of note as the entire study population received prophylactic low dose aspirin as part of the standard of care in this setting to minimize just such events. Given the emerging concern over a possible pro-thrombotic action of certain agents in the COX2 class, these data are of concern." Elsewhere Dr. Johnson states, "manifestations of an increase in vascular events rates (sp.), which coupled with the signals seen elsewhere in this database...all contributes to the concern that there may be a component of increased thrombogenicity associated with this agent."¹³ In the published version, Ott *et al* discloses a substantial increase of all serious adverse events in the parecoxib/valdecoxib group versus placebo (19.0% versus 9.9%, p=0.015). This was partially due to a trend towards more deaths, MIs, cerebrovascular disorders, and renal events in the study group. Although none of these individual adverse events reached statistical significance, the authors reported, "The incidence of both cardiovascular and cerebrovascular SAEs [serious adverse events] was proportionally, but not significantly, greater in P/V [parecoxib/valdecoxib] group patients than in control patients, potentially implicating a thrombosis-mediated association with COX-2 inhibitor use." They also said, "Our trial...was not powered to detect differences for specific SAEs."¹⁴

A significantly greater frequency of cardiovascular/thromboembolic events, such as MI, ischemia, cerebrovascular accident, deep vein thrombosis, and pulmonary embolism, was also observed in the valdecoxib/parecoxib group in the post-CABG Trial #2 compared to placebo, 2.0% valdecoxib/parecoxib vs. 0.5%.¹⁵ A statistically significant excess of surgical wound complications, including deep infections and healing events, was also noticed in both post-CABG trials. However, a study involving orthopedic or general surgery patients revealed no significant differences in the overall safety profile.¹⁵

Furberg *et al* just published a meta-analysis of the two post-CABG trials included in the valdecoxib package insert. Individually, the two studies were not powered to achieve statistical significance. However, when the two studies were combined they achieved statistical significance for the cardiovascular outcome, without any evidence of heterogeneity. The relative risk of cardiovascular events in the treatment group versus placebo was 3.08 (95% CI 1.20-7.87.). The authors concluded, "In the absence of evidence of safety, it is prudent to avoid the use of valdecoxib altogether or use it only as a drug of last resort. The recent emergence of a cardiovascular hazard with a third, structurally distinct COX-2 inhibitor—celecoxib—provides compelling evidence that these adverse coronary and cerebrovascular events represent a class effect, as originally predicted." They also proffered an explanation for the negative post-general surgery study, "A PGI₂ based mechanism would be facilitated by the presence of hemostatic activation, such as CABG surgery."¹⁶ The post-CABG trials achieved such striking results because they were conducted in extremely high-

¹³ Johnson K. Valedcoxib. Food and Drug Administration Medical Officer Review November 7, 2001, NDA 21,341.

¹⁴ Ott E, Nussmeier NA, Duke PC et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2003; 125:1481-92.

¹⁵ Bextra. Package insert. New York City, NY. Pfizer, Inc., Nov 2004. (Accessed Jan 4, 2005 at www.pfizer.com/download/uspi_bextra.pdf)

¹⁶ Furberg CD, Psaty BM, and FitzGerald GA. Parecoxib, valdecoxib, and cardiovascular risk. *Circulation* 2005; 111:249.

risk patients, thereby uncovering the underlying risk of selective COX-2 inhibition not as apparent in the post-general surgery study.

The package labeling for Bextra states, "Randomized controlled clinical trials with BEXTRA longer than one year have not been conducted, nor have studies powered to detect differences in cardiovascular events in a chronic setting been conducted."¹⁵ As this says, despite the increased cardiovascular risk documented with both other members of this class and seen with valdecoxib in the post-CABG trials, valdecoxib trials have been limited to time periods inadequate to fully address the dangers of chronic use for which it is approved.

Lumiracoxib (Prexige)

Lumiracoxib is a COX-2 inhibitor that is still in the development stage. Although lumiracoxib has not yet been approved by the FDA and is not a subject of this petition, we will discuss the currently available clinical trial data to assist in proving that there exists a class effect for the cardiotoxicity of all COX-2 inhibitors. The TARGET study of reduction in ulcer complications and cardiovascular outcomes published in the *Lancet* in 2004 followed 18,325 patients on lumiracoxib, naproxen, or ibuprofen for one year.¹⁷ Lumiracoxib had higher rates for several cardiovascular events compared to the combined NSAID group: clinical myocardial infarctions 0.20% vs. 0.07%, fatal stroke 0.05% vs. 0.02%, and ischemic stroke 0.25% vs. 0.19%. This difference was magnified in the substudy comparing lumiracoxib to naproxen: clinical myocardial infarctions 0.28% vs. 0.06%, fatal stroke 0.06% vs. 0.02%, and ischemic stroke 0.32% vs. 0.23%.¹⁸ The data show a consistent and unequivocal, although not statistically significant, trend of an increased risk of cardiovascular morbidity with lumiracoxib. A commentary in the same issue mentioned, "The statistical power of TARGET is inadequate to detect significant differences in rates of myocardial infarction... Findings from TARGET reinforce the concept that naproxen provides some anti-thrombotic protective effect, but do not clearly exonerate this or other coxibs from potentiating myocardial infarctions."¹⁹

Etoricoxib (Arcoxia)

Etoricoxib is a new COX-2 inhibitor in development by Merck whose structure is closely related to Vioxx. We will discuss the currently available clinical trial data for the same reason as lumiracoxib. An elevation of cardiovascular risk was seen with etoricoxib in the EDGE trial. In this study, 7111 patients were randomized to receive either etoricoxib or diclofenac for one year to investigate GI toxicity. EDGE has not been published yet, but some of the results were presented in poster format at the American College of Rheumatology meeting in Oct 2004. The tendency towards more cardiac and cerebral events in the etoricoxib group vs. the diclofenac group includes the categories of all cardiac events (0.97 event rate vs. 0.73

¹⁷ Schnitzer TJ, Burmester GR, Mysler E et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004; 364: 665-74.

¹⁸ Parkouh ME, Kirshner H, Harrington RA et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* 2004; 364: 675-84.

¹⁹ Topol EJ and Falk GW. A coxib a day won't keep the doctor away. *Lancet* 2004; 364: 639-40.

event rate), acute myocardial infarction (0.68 event rate vs. 0.42 event rate), and sudden cardiac death (0.07 event rate vs. 0.04 event rate). While these differences were not statistically significant, previous trials showed the relative risk of cardiovascular events for etoricoxib over naproxen to be 1.7, a comparable rate to the 2.0 relative risk of rofecoxib vs. naproxen seen in VIGOR. In fact, "Merck officials and researchers have been unable to offer any explicit ways in which Arcoxia is different from Vioxx that might suggest why Arcoxia shouldn't have the same cardiovascular risk as Vioxx," disclosed a health news reporter in a recent article after interviewing several Merck officials.²⁰

Three much shorter trials designed to determine efficacy in treating osteoarthritis and rheumatoid arthritis symptoms also exhibit a trend towards increased cardiovascular risk. One trial of osteoarthritis patients involving 617 patients consisted of two parts. The first compared various doses of etoricoxib (5, 10, 30, 60, or 90 mg/day) to each other and placebo over six weeks. The second part changed the participants to either etoricoxib at 30, 60, or 90 mg/day or diclofenac and lasted 8 weeks. The only four patients with serious cardiovascular adverse experiences were clustered in the groups with doses of etoricoxib at and above 30 mg/day.²¹ In a multi-national trial, 687 rheumatoid arthritis patients were given etoricoxib, naproxen, or placebo for 12 weeks. There were two confirmed cardiovascular thrombotic adverse events on etoricoxib contrasted with one on placebo and none on naproxen.²² A trial of 816 rheumatoid arthritis patients conducted solely in the United States also compared etoricoxib to placebo and naproxen and recorded two confirmed, adjudicated cardiovascular adverse events on etoricoxib but none in the other groups.²³

Although we agree with the authors from the multi-national rheumatoid arthritis trial who wrote, "No meaningful conclusions about the overall cardiovascular safety of etoricoxib can be determined from this single study"²², a consistent trend towards increased cardiovascular risks in all of these studies taken in the context of the greater hazard illustrated with all COX-2 inhibitors paints a telling picture.

Other Cardiovascular Risks of COX-2 inhibitors

Hypertension

Valdecoxib (Bextra) increased the rates of edema and hypertension in a study covered in the FDA review involving 1217 patients taking either valdecoxib or naproxen over 6 months. The naproxen 1000mg/day group had edema in 0.5% and worsening BP in 3.1%. However, the valdecoxib 40mg/day group had edema in 1.5% and worsening blood pressure [BP] in

²⁰ Peterson, L. The cardiovascular safety of COX-2 inhibitors. Trends-in-Medicine Nov 2004.

²¹ Gottesdiener K, Schnitzer T, Fisher C et al. Results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis. Rheumatology 2002; 41:1052-61.

²² Collantes E, Curtis SP, Lee KW et al. A multinational randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis. BMC Family Practice 2002; 3:1-10.

²³ Matsumoto AK, Melian A, Mandel DR et al. A randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis. J Rheumatol 2002; 29:1623-30.

6.0% of patients. The valdecoxib 80mg/day group had edema in 2.2% and worsening BP in 7.7%. FDA Medical Officer Dr. Johnson says, "The safety profile with chronic use in RA and OA [rheumatoid arthritis and osteoarthritis] is adequate at 10mg/d. At higher total daily doses, the findings of more hypertension and edema are frequently reproduced, and they are formally affirmed in a prospective manner in Trial 47 which directly tested the hypothesis of renal safety at 40 and 80 mg/day."¹³

Heart Arrhythmias

In the CLASS trial already discussed, combined atrial serious adverse events, such as atrial arrhythmias, a slow heart rate, or atrial fibrillation, were found more often in the celecoxib group, 0.6%, than in the diclofenac group, 0.2%, or the ibuprofen group, 0.4%. When the analysis by aspirin use was completed, the group of non-aspirin users taking celecoxib also had a higher rate of atrial fibrillation, 0.3%, compared to both diclofenac and ibuprofen users which had 0.1%. Dr. Throckmorton commented, "The observed differences in the rates of atrial arrhythmias are derived from small numbers of patients and lack supportive evidence from other sources (*e.g.*, animal models, post-marketing data) and their clinical relevance cannot be determined. . . . The data suggesting an increased rate of supraventricular arrhythmias in patients taking celecoxib compared to diclofenac and ibuprofen are provocative but require additional investigation."⁷ This additional investigation, in the form of a randomized control trial large enough to determine if a difference in cardiovascular arrhythmias exists, has not been done.

Proposed Mechanism for Increased Cardiovascular Risk of COX-2 Inhibitors

Pro-thrombotic Effect on Prostaglandins

Two vasoactive prostaglandins balance pro-thrombotic and anti-thrombotic forces in the body. Prostaglandin I₂ (PGI₂) dilates blood vessels, inhibits platelet aggregation, and prevents the proliferation of vascular smooth-muscle cells in vitro, a series of effects that collectively decrease the propensity to thrombosis. Research confirms that PGI₂ is largely a product of the enzyme COX-2 which is induced in the lining of blood vessels.^{24, 25} On the other hand, thromboxane A₂ (TxA₂) is formed by COX-1 present in platelets and enhances platelet aggregation, vasoconstriction, and vascular proliferation in response to injury, thereby increasing the likelihood of thrombosis.²⁵

The importance of this defensive homeostatic mechanism was emphasized by Cheng et al in experiments with knock-out mice. Deleting the receptor for PGI₂ enhanced TxA₂ synthesis, the proliferative response of the blood vessel lining, and the percentage of luminal stenosis (narrowing of the blood vessel due to this proliferation of the blood vessel lining) after injury. The opposite was seen in mice lacking the TxA₂ receptor. However, there was no change

²⁴ FitzGerald GA. COX-2 and beyond: approaches to prostaglandin inhibition in human disease. *Nat Rev Drug Discov* 2003; 2: 879-90.

²⁵ FitzGerald GA. Coxibs and cardiovascular disease. *N Engl J Med* 2004; 351: 1709-11.

from wild type in mice missing both receptors.²⁶ The key nature of this balance was reaffirmed in experiments by Buerkle *et al* using human platelets in a hamster arteriole model. They found that COX-2 inhibition significantly increased platelet-vessel wall interactions and firm adhesions except when it was offset by concurrent COX-1 inhibition with aspirin. Selective inhibition of COX-2 also accelerated the occlusion of the vessel after the vessel wall was damaged. The authors stated, "The proadhesive effects of selective Cox-2 inhibition in intact arterioles of even healthy animals and the rapid occlusion of injured vessels argue in favor of cautious use of these compounds in patients at cardiovascular risk."²⁷

Non-selective NSAIDs inhibit both forms of the enzyme, maintaining the clotting equilibrium. Low-dose aspirin, known to have an anti-thrombotic effect, largely inactivates the platelet COX-1, thereby reducing only the levels of TxA₂ and decreasing blood clotting.²⁸ Conversely, selective inhibition of COX-2 prevents the synthesis of PGI₂, leaving the pro-thrombotic TxA₂ unopposed. McAdam *et al* demonstrated that the urinary metabolite of PGI₂ declines significantly when either ibuprofen (a non-selective COX inhibitor) or celecoxib is taken by young, healthy adults, but only ibuprofen decreases the level of the urinary metabolite of TxA₂.²⁹ Interestingly, excess TxA₂ is associated with a higher risk of major vascular events in patients with peripheral arterial obstructive disease.²⁸ Conversely, syndromes of platelet activation (such as unstable angina, severe atherosclerosis, and angioplasty procedures) elevate excretion of the urinary metabolite of PGI₂ in patients as if to modulate the pro-thrombotic response to vascular injury.²⁹ It is of note that diminished function of PGI₂ does not generate spontaneous thrombosis, only an increased response to a thrombotic trigger.²⁴

Dr. FitzGerald wrote, "Thus, a single mechanism, depression of prostaglandin I₂ formation, might be expected to elevate blood pressure, accelerate atherogenesis, and predispose patients receiving coxibs to an exaggerated thrombotic response to the rupture of an atherosclerotic plaque."²⁵ Another review stated, "Although an effect of this magnitude [the difference in major cardiovascular events in the VIGOR trial] would be surprising, it would be consistent with the formation of thromboxane in the absence of the concomitant generation of prostacyclin. This would be a drug-class—specific effect, but a difference in rates of cardiovascular events may not have been revealed in the CLASS trial because of differences in the study patients, the use of aspirin by some patients, or the nature of the nonselective NSAIDs used in the two trials."³⁰

COX-2 Inhibitor Prevention of Protective Cardiac Response

²⁶ Cheng Y, Austin SC, Rocca B et al. Role of prostacyclin in the cardiovascular response to thromboxane A₂. *Science* 2002; 296: 539-41.

²⁷ Buerkle MA, Lehrer S, Sohn HY et al. Selective inhibition of cyclooxygenase-2 enhances platelet adhesion in hamster arterioles in vivo. *Circulation* 2004; 110: 2053-9).

²⁸ Catella-Lawson F and Crofford LJ. Cyclooxygenase inhibition and thrombogenicity. *Am J Med* 2001; 110(3A): 28S-32S.

²⁹ McAdam BF, Catella-Lawson F, Mardini IA et al. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: The human pharmacology of a selective inhibitor of COX-2. *Proc Natl Acad Sci USA* 1999; 96: 272-7.

³⁰ FitzGerald GA and Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med*, 2001; 345:433-42.

The term cardiac preconditioning refers to the phenomenon whereby if the heart muscle is exposed to various stimuli (such as mild ischemia [lack of adequate blood flow], pharmacologic triggers, volatile anesthetics, or physical exercise) there is a reduction of the danger to those cells if confronted by later, more prolonged ischemia. Human studies have shown that cardiac preconditioning is a clinically significant protection against myocardial infarction and death—decreasing the infarction size, post-infarction arrhythmias, and other life-threatening complications as well as increasing the remaining cardiac function.^{31,32} Patients with pre-infarction angina (a clinical equivalent of cardiac preconditioning) suffered less serious heart attacks. COX-2 inhibition has been shown to prevent cardiac preconditioning, increasing myocardial stunning and infarction size in multiple animal models.^{33,34,35} Two of these studies used celecoxib as the selective COX-2 inhibitor. The authors of one of these studies concluded that the COX-2 enzyme is a “cardioprotective protein.”³⁵ In comparison, aspirin at doses that inhibit COX-1 selectively did not alter preconditioning.³⁶ COX-2-dependent prostaglandins also alleviate myocardial cell destruction resulting from oxidative damage due to exposure to the cancer chemotherapy drug doxorubicin or hydrogen peroxide.^{37,38} All of this evidence points to the conclusion that COX-2 inhibition will not only predispose patients to thrombosis, thus causing heart attacks, but it will also worsen the severity of their heart attacks.

Other Risks of COX-2 Inhibition

The scientific community initially believed that COX-2 was exclusively an induced enzyme that functioned only in pathologic states, the opposite of the constitutively expressed COX-1 which maintains homeostasis. This concept is what fueled the search for selective COX-2 inhibitors which would theoretically avoid the adverse effects of nonselective NSAIDs. Further research, however, has somewhat blurred this distinction as studies found constitutive expression of COX-2 in tissues such as kidney and brain and physiological induction of COX-2 in the ovary, blood vessel lining, and bone.³⁹ Dr. Lipsky *et al* asserted

³¹ Shiraki H, Yoshikawa T, Anzai T et al. Association between preinfarction angina and a lower risk of right ventricular infarction. *N Engl J Med* 1998; 338:941-7.

³² Kloner RA, Shook T, Przyklenk K et al. Previous angina alters in-hospital outcome in TIMI 4—A clinical correlate to preconditioning? *Circulation* 1995; 91:37-45.

³³ Alcindor D, Krolkowski JG, Pagel PS, Warltier DC, Kersten JR. Cyclooxygenase-2 mediates ischemic, anesthetic, and pharmacologic preconditioning in vivo. *Anesthesiology* 2004; 100:547-54.

³⁴ Shinmura K, Tang XL, Wang Y, Xuan YT, Liu SQ, Takano H, Bhatnagar A, Bolli R. Cyclooxygenase-2 mediates the cardioprotective effects of the late phase of ischemic preconditioning in conscious rabbits. *Proc Natl Acad Sci USA* 2000; 97:10197-202.

³⁵ Guo Y, Bao W, Wu WJ, Shinmura K, Tang XL, Bolli R. Evidence for an essential role of cyclooxygenase-2 as a mediator of the late phase of ischemic preconditioning in mice. *Basic Res Cardiol* 2000; 95:479-84

³⁶ Shinmura K, Kodani E, Xuan YT et al. Effect of aspirin on late preconditioning against myocardial stunning in conscious rabbits. *J Am Coll Cardiol* 2003; 41:1183-94.

³⁷ Adderley SR and Fitzgerald DJ. Oxidative damage of cardiomyocytes is limited by extracellular regulated kinases 1/2-mediated induction of cyclooxygenase-2. *J Biol Chem* 1999; 274: 5038-46.

³⁸ Dowd NP, Scully M, Adderley SR et al. Inhibition of cyclooxygenase-2 aggravates doxorubicin-mediated cardiac injury in vivo. *J Clin Invest* 2001; 108:585-90.

³⁹ Lipsky PE, Brooks P, Crofford LJ et al. Unresolved issues in the role of cyclooxygenase-2 in normal physiologic processes and disease. *Arch Intern Med* 2000; 160: 913-20.

this view, "Evolving knowledge of the biologic function of COX-1 and COX-2 has suggested that the initial paradigm is an oversimplification. Although COX-2 is induced at sites of inflammation, a critical role for COX-2 in a number of other physiologic processes has emerged....These findings have provided a more complex model of the interplay of COX-1 and COX-2 in both normal physiologic processes and in pathophysiologic conditions than the homeostasis vs inflammation paradigm of COX-1 and COX-2 action originally suggested."³⁹

Evidence exists that COX-2 fulfills a necessary role in maintaining renal function and modulating neural responses. This would predict that disturbances in electrolyte levels would result from COX-2 inhibition,⁴⁰ which was seen in clinical trials as an increase in the rate of hyperkalemia.⁷ "Studies with COX-2—null mice [mice missing this enzyme] have documented reproductive failures at ovulation, fertilization, implantation, and decidualization....Inhibition of COX-2 by NSAIDs may explain the infertility secondary to delayed or blocked follicular rupture associated with their use."^{39,41} Preliminary indications point to an important component of the healing inflammatory response requiring the activity of COX-2. Besides the markedly increased incidence of sternal wound complications seen in post-CABG patients who were using valdecoxib¹⁵, COX-2 inhibitors impair ulcer healing in mice and it has been shown that COX-2 is selectively expressed in the margins of healing ulcers.³⁰ Because COX-2 is known to serve important functions in healthy patients as well as causing an inflammatory response, its disruption would be expected to block these necessary tasks as well.

NSAIDs and Cancer

There are many studies in which NSAIDs have been employed to try to prevent cancer of various kinds. Among the most successful are one study in which an NSAID was used to prevent recurrence of colon polyps in patients with previous colon cancer⁴² and another study in which patients with one previous adenomatous colon polyp had reduced future occurrence of additional polyps when they took an NSAID.⁴³ In both of these studies the NSAID employed was aspirin with the additional advantage of protection against, instead of increasing, cardiovascular risk (as seen with celecoxib and valdecoxib). Although celecoxib is approved for reducing polyps in people with an inherited disease, familial adenomatous polyposis (FAP), the need for repeat colonoscopy in these patients significantly lessens any advantage of taking celecoxib as does the increased cardiovascular risk of the drug. An older NSAID, sulindac, has also been found effective in regression of polyps in patients with FAP.⁴⁴

⁴⁰ Catella-Lawson F, McAdam B, Morrison BW et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. *J Pharmacol Exp Ther* 1999; 289: 735-41.

⁴¹ Lim H, Paria BC, Das SK et al. Multiple female reproductive failures in cyclooxygenase 2-deficient mice. *Cell* 1997; 91: 197-208.

⁴² Sandler RS et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *New Eng J Med* 2003;348:883-90.

⁴³ Baron JA et al. A randomized trial of aspirin to prevent colorectal adenomas. *New Eng J Med*. 2003;348:891-9.

⁴⁴ Nugent KP, Farmer KC, Spigelman AD, Williams CB, Phillips RK. Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. *Br J Surg*. 1993 Dec;80:1618-9.

Celecoxib and Valdecoxib: the Risk Outweighs the Benefits

In conclusion, we review the risk to benefit ratio for celecoxib and valdecoxib. In theory, potential benefits for these drugs could be achieved in either effectiveness or safety. However, neither drug has demonstrated increased efficacy over conventional NSAID therapy. Among the 14 studies we reviewed, six with active comparators reported efficacy information. In five of the six, there was no difference between the COX-2 inhibitor and other NSAIDs. In the etoricoxib trial with rheumatoid arthritis in the U.S., there was a claim of increased efficacy which was not replicated in the multi-national trial of etoricoxib in rheumatoid arthritis patients. Similarly, neither drug has exhibited a decrease in clinically significant upper GI events. The only drug the FDA certified to do so was Vioxx, and it was removed from the market for its cardiovascular toxicity. Therefore, no unique advantages for either celecoxib or valdecoxib exist.

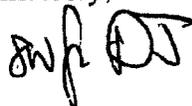
On the other hand, statistically significant increased cardiovascular risk has been demonstrated in every COX-2 inhibitor that has been approved. The two celecoxib trials that do not show an increased risk, PreSAP and ADAPT, have not been published; so we have been unable to evaluate the data for a trend similar to that seen in CLASS. The negative post-general surgery trial with valdecoxib only lasted for 10 days in relatively low-risk patients. Most randomized control trials were not large enough to definitely evaluate the cardiovascular risk and therefore they demonstrate consistent trends towards an increased risk which do not achieve statistical significance. The longer APC trial of celecoxib in low risk patients and the two short post-CABG trials of valdecoxib in high risk patients all reached statistical significance. We also presented a plausible mechanism for the increased cardiovascular risk being due to a class effect. Therefore, celecoxib and valdecoxib/parecoxib present a unique risk with no unique benefits. As the Acting Deputy Commissioner for Operations at the FDA Dr. Janet Woodcock said at a recent American College of Rheumatologists meeting, "Coxibs are among the most toxic drugs for a non-life threatening indication. They have hepatotoxicity, CV toxicity, renal toxicity, etc."³

Some advocates of COX-2 inhibitors have noted that the apparent cardiovascular problems are alleviated at least partially by taking low-dose aspirin concurrently. The only evidence we could find for this was the low-dose aspirin subgroup post hoc analysis of the CLASS data. This claim has not been assessed in the setting of a prospective randomized control trial. However, even if it were correct, taking low-dose aspirin concurrently negates any potential protective effect on upper GI perforations or bleeding. Dr. Topol and Dr. Falk wrote in their recent review in the Lancet, "For patients taking low-dose aspirin, it is hard to justify the coxib: there is no benefit in ulcer complication reduction, but the risk of myocardial infarction and hepatotoxicity persist."¹⁹

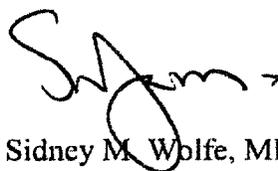
Changing the package labeling to address this increased cardiovascular risk is not enough. Both the APPROVe and the APC studies were conducted in patients with a level of cardiovascular risk equivalent to that in the general population. Both trials revealed statistically significant increases in cardiovascular events. Therefore, even low risk patients are subject to the increased danger and there is no safe population for use of these drugs. We

strongly urge you to immediately remove celecoxib (Celebrex) and valdecoxib (Bextra) from the market for the sake of patients' safety and halt all plans to approve lumiracoxib and etoricoxib because of their cardiovascular risks.

Sincerely,



Dawn Jennings-Peterson, Staff Researcher



Sidney M. Wolfe, MD
Director, Public Citizen's Health Research Group

Studies Examining Cardiovascular Risk with COX-2 Inhibitors			
Studies	Findings	Comparators	References
Rofecoxib			
VIGOR GI toxicity 9 mos 8076 pts	Statistically significant fourfold increase in MI risk from 0.1% to 0.4% Double the rate of all serious thrombotic cardiovascular adverse events* RR 2.38 (95% CI 1.39-4.00) Fivefold increase in serious thrombotic cardiovascular adverse events* in patients with previous cardiovascular history§ who were not taking low-dose aspirin RR 4.89 (95% CI 1.41-16.88)	Naproxen	Bombardier C, Laine L, Reicin A et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. <i>N Engl J Med</i> 2000; 343:1520-8. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. <i>JAMA</i> 2001; 286:954-9.
APPROVe polyp prevention 3 yrs 2600 pts	Double the risk of any thrombotic cardiovascular event RR 1.96, p=0.007 Double the risk of an MI after 18 months of treatment (3.5% vs. 1.9% placebo)	Placebo	Merck & Co., Inc News Release. Merck announces voluntary worldwide withdrawal of Vioxx. Sept 30, 2004. (Accessed Jan 4, 2005 at www.vioxx.com/rofecoxib/vioxx/consumer/index.jsp) FDA News. FDA issues public health advisory on Vioxx as its manufacturer voluntarily withdraws the product. Sept 30, 2004. (Accessed Jan 4, 2005 at www.fda.gov/bbs/topics/news/2004/NEW01122.html) News Interactive. Arthritis drug 'a killer'. Dec 18, 2004. (Accessed Jan 5, 2005 at www.news.com.au/common/story_page/0,4057,11720748%255E3102,00.html) Peterson, L. The cardiovascular safety of COX-2 inhibitors. <i>Trends-in-Medicine</i> Nov 2004

Celecoxib			
<p>CLASS</p> <p>GI toxicity</p> <p>1 yr 8059 pts</p>	<p>A tendency toward more combined anginal cardiac adverse events 1.4% vs. 1.0% ibuprofen or diclofenac</p> <p>Increased combined anginal disorders in patients not receiving aspirin 0.6% vs. 0.2% diclofenac and 0% ibuprofen</p> <p>Increased combined atrial serious cardiac adverse events in patients not receiving aspirin 0.3% vs. 0.1% diclofenac and 0% ibuprofen</p> <p>Double the rate of MI in patients not receiving aspirin 0.2% vs. 0.1% ibuprofen or diclofenac</p>	<p>Ibuprofen Diclofenac</p>	<p>Throckmorton DC. Comparative safety of celecoxib, diclofenac, and ibuprofen. Food and Drug Administration Memorandum Jan 5, 2001</p>
<p>APC</p> <p>polyp prevention</p> <p>3 yrs ~2000 pts</p>	<p>Statistically significant 2.5 times the risk of cardiovascular eventsΨ at a dose of 400mg/day</p> <p>Statistically significant 3.4 times the risk of cardiovascular eventsΨ at a dose of 800mg/day</p>	<p>Placebo</p>	<p>Pfizer Inc News Release. Pfizer statement on new information regarding cardiovascular safety of Celebrex. Dec 17, 2004. (Accessed Jan 4, 2005 at www.celebrex.com/cardiovascular_safety_of_celebrex_tp.asp)</p> <p>FDA Alert for Practitioners. Celebrex (celecoxib). Dec 17, 2004. (Accessed Jan 4, 2005 at www.fda.gov/cder/drug/infopage/celebrex/celebrex-hcp.pdf)</p>
<p>PreSAP</p> <p>polyp prevention</p> <p>3 yrs 1600pts</p>	<p>No statistically significant increased cardiovascular risk at a dose of 400mg/day</p>	<p>Placebo</p>	<p>Pfizer Inc News Release. Pfizer statement on new information regarding cardiovascular safety of Celebrex. Dec 17, 2004. (Accessed Jan 4, 2005 at www.celebrex.com/cardiovascular_safety_of_celebrex_tp.asp)</p> <p>FDA Statement. FDA statement on the halting of a clinical trial of the Cox-2 inhibitor Celebrex. Dec 17, 2004. (Accessed Jan 4, 2005 at www.fda.gov/bbs/topics/news/2004/new01144.html)</p>

ADAPT Alzheimer's prevention 3yrs 2400 pts	No statistically significant increased cardiovascular risk at a dose of 400mg/day	Naproxen Placebo	Pfizer Inc News Release. Pfizer says new NIH study results are consistent with large body of evidence supporting cardiovascular safety of Celebrex. Dec 21, 2004. (Accessed Jan 4, 2005 at www.pfizer.com/are/news_releases/2004pr/mn_2004_1221.html)
Valdecoxib/Parecoxib			
Post-CABG Trial #1 post-op pain 14 days 462 pts	Excess serious cardiovascular thromboembolic events ∞ and death despite prophylactic low-dose aspirin 25.7% vs. 15.2% placebo Significantly greater incidence of cardiovascular/thromboembolic events Φ 4.8% vs. 1.3% in placebo Twofold increase in MI 2.6% vs. 1.3% placebo	Placebo	Bextra. Package insert. New York City, NY. Pfizer, Inc., Nov 2004. (Accessed Jan 4, 2005 at www.pfizer.com/download/uspi_bextra.pdf) Ott E, Nussmeier NA, Duke PC et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg 2003; 125:1481-92. Johnson K. Valdecoxib. Food and Drug Administration Medical Officer Review Nov 7, 2001; NDA 21,341
Post-CABG Trial#2 post-op pain 10 days 1636 pts	A significantly greater incidence of events in the cardiovascular/ thrombolic category 2.0% vs 0.5% in placebo	Placebo	Bextra. Package insert. New York City, NY. Pfizer, Inc., Nov 2004. (Accessed Jan 4, 2005 at www.pfizer.com/download/uspi_bextra.pdf)
Post-General Surgery post-op pain 10 days 1050 pts	No significant differences in the overall safety profile	Placebo	Bextra. Package insert. New York City, NY. Pfizer, Inc., Nov 2004. (Accessed Jan 4, 2005 at www.pfizer.com/download/uspi_bextra.pdf)

Lumiracoxib			
TARGET GI toxicity 1 yr 18,325 pts	A consistent and unequivocal trend of additional cardiovascular events: Clinical MI 0.20% vs. 0.07% Fatal stroke 0.05% vs. 0.02% Ischemic stroke 0.25% vs. 0.19%	Naproxen Ibuprofen	Farkouh ME, Kirshner H, Harrington RA et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: a randomized controlled trial. Lancet 2004; 364: 675-84.
Etoricoxib			
EDGE GI toxicity 1 yr 7,111 pts	An elevated relative risk of several cardiovascular events: All cardiac events 0.97 vs. 0.73 Acute MI 0.68 vs. 0.42 Sudden cardiac death 0.07 vs. 0.04	Diclofenac	Peterson, L. The cardiovascular safety of COX-2 inhibitors. Trends-in-Medicine Nov 2004
Osteoarthritis efficacy 14 wks 617 pts	Four patients with serious cardiovascular adverse experiences† in the 30mg, 60mg, or 90mg group vs. none in the placebo, diclofenac, 5 mg, or 10mg groups	Placebo Diclofenac	Gottesdiener K, Schnitzer T, Fisher C et al. Results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis. Rheumatology 2002; 41:1052-61.
Rheumatoid Arthritis Multi-national efficacy 12 wks 687 pts	Two confirmed cardiovascular thrombotic adverse events on etoricoxib vs. 1 on placebo and none for naproxen	Placebo Naproxen	Collantes E, Curtis SP, Lee KW et al. A multinational randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis. BMC Family Practice 2002; 3:10.

<p>Rheumatoid Arthritis U.S. efficacy</p> <p>12 wks 816 pts</p>	<p>Two confirmed adjudicated cardiovascular adverse events on etoricoxib vs. none in the other groups</p>	<p>Placebo Naproxen</p>	<p>Matsumoto AK, Melian A, Mandel DR et al. A randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis. J Rheumatol 2002; 29:1623-30.</p>
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* Serious thrombotic cardiovascular adverse events include MI, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden unexplained death, ischemic stroke, and transient ischemic attack

§ Previous cardiovascular history defined as past medical history of cerebrovascular accident, transient ischemic attack, MI, unstable angina, angina pectoris, coronary artery bypass graft surgery, or percutaneous coronary interventions

Ψ Cardiovascular events are comprised of cardiovascular death, acute MI, and stroke

∞ Serious cardiovascular thromboembolic events include MI, cerebrovascular accident, deep venous thrombosis, pulmonary embolism, congestive heart failure, and renal dysfunction or failure

Φ Cardiovascular/thromboembolic events consist of MI, ischemia, cerebrovascular accident, deep vein thrombosis, and pulmonary embolism

† Serious cardiovascular adverse experiences include deep venous thrombosis, chest pain associated with angina pectoris and atrial fibrillation, atrial fibrillation, and ventricular tachycardia



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Joan Claybrook, President

January 26, 2005

**ADDENDUM TO CITIZEN'S PETITION TO REMOVE THE COX-2 INHIBITORS
CELECOXIB (CELEBREX) AND VALDECOXIB (BEXTRA) FROM THE MARKET**

Environmental Impact Statement

Nothing requested in this petition will have an impact on the environment.

Certification Statement

The undersigned certifies that, to their best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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