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THESIS

**CARDIOVASCULAR RISK COMPARISONS OF NON-
STEROIDAL ANTI-INFLAMMATORY AGENTS IN THE
TRICARE**

by

Kim L. Lefebvre

September 2005

Thesis Advisor:
Second Reader:

Samuel E. Buttrey
Lyn R. Whitaker

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INFLAMMATORY AGENTS IN THE TRICARE POPULATION**

Kim L. Lefebvre
Commander, United States Navy
B. S., University of Rhode Island, 1985
Pharm D., Idaho State University, 1999
M. B. A., Southern New Hampshire University, 2004

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requirements for the degree of

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**NAVAL POSTGRADUATE SCHOOL
September 2005**

Author: Kim L. Lefebvre

Approved by: Samuel E. Buttrey
Thesis Advisor

Lyn R. Whitaker
Second Reader

James N. Eagle
Chairman, Department of Operations Research

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ABSTRACT

This report examines differences in risk of myocardial infarction and stroke (cardiovascular events) between cyclooxygenase-2 (COX-2) inhibitors rofecoxib, celecoxib and valdecoxib, and the traditional nonsteroidal anti-inflammatory agents (NSAIDs) naproxen and ibuprofen as well as meloxicam, a preferential COX-2 inhibitor. The population studied was the DoD TRICARE beneficiary population of age greater than 40 during the study period. In September of 2004, Rofecoxib, a COX-2 inhibitor was removed from the market due to an increased risk of cardiovascular events. In February of 2005, the Food and Drug Administration (FDA) examined the entire class of COX-2 inhibitors and recommended that Valdecoxib also be withdrawn from the market. According to Department of Defense TRICARE prescription records, COX-2 inhibitor prescription numbers were increasing rapidly and more than \$7 million was spent on these agents alone in July of 2004. Logistic regression was used to analyze TRICARE prescription and diagnosis data from calendar years 2002, 2003, and 2004 for cardiovascular event risk comparisons among various NSAIDs. Rofecoxib, was found to have a significantly increased risk of cardiovascular events when compared with all other medications in the study, including Valdecoxib. Odds ratios for comparison with Valdecoxib, Celecoxib, Meloxicam, Ibuprofen and Naproxen are: 1.09, 1.14, 1.15, 1.28, and 1.23. Valdecoxib showed a significant increase compared to ibuprofen, naproxen and celecoxib (Odds Ratios 1.21, 1.16 and 1.06). Ibuprofen showed a significantly decreased risk relative to all medications except naproxen. When considering only cardiovascular risk, this study suggests prescribers should consider ibuprofen or naproxen as the primary agent of choice, with meloxicam, and celecoxib as reasonable second choices. Ultimately, the decision must also weigh the patient's risk of gastrointestinal side effects and cost of therapy.

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Executive summary

In September of 2004 Merck and Co. voluntarily withdrew their non-steroidal anti-inflammatory product, Vioxx, from the market due to mounting evidence that it placed users at an increased risk of cardiovascular events such as myocardial infarction and stroke. This prompted an extensive review of all non-steroidal anti-inflammatory agents by the Food and Drug Administration (FDA), with a subsequent recommendation that Pfizer remove its product, Bextra, from the market as well. Additionally, the FDA mandated that all remaining agents carry new and stronger warnings regarding the potential for serious adverse cardiovascular events in addition to the warnings of life threatening gastrointestinal bleeding.

At the time Vioxx and Bextra were removed from the market, DoD TRICARE beneficiaries were filling more than 60,000 prescriptions per month for Vioxx and another 45,000 per month for Bextra. Military Treatment Facility expenditures were more than \$7 million per month for Vioxx, Bextra and Celebrex alone. This cost does not include prescriptions obtained from other TRICARE network sources such as retail or mail order outlets.

This study aims to determine differences in cardiovascular risk among the most popular non-steroidal anti-inflammatory agents, including those that were removed from the market. Results can be used as part of a complete cost benefit analysis of products in this class, and the information used as a basis for safe prescribing.

The study was performed using TRICARE prescription records from calendar years 2002, 2003, and 2004. Patients of age greater than 40 years who received at least one prescription for Motrin (ibuprofen), Vioxx (rofecoxib), Bextra (valdecoxib), Celebrex (celecoxib), Naprosyn (naproxen), or Mobic (meloxicam) were entered into the study. All events of myocardial infarction and stroke were also obtained for this same period. Prescription records were cross-matched with the event file and a determination was made whether or not to associate an event with a prescription. A logistic regression model was used to determine odds ratios of events among the various prescription

medications. Variables in the following model included the category of the beneficiary, age, product, and dosing, which was categorized as either high or low.

$$\log\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta_1 age_i + \beta_3 med_i + \beta_4 dose_i + \beta_5 bencat_i$$

Upon analysis, rofecoxib (Vioxx), was found to have a significantly increased risk of cardiovascular events when compared with all other medications in the study, including Valdecoxib (Bextra). Odds ratios for comparison with Valdecoxib, Celecoxib, Meloxicam, Ibuprofen and Naproxen are: 1.09, 1.14, 1.15, 1.28, and 1.23. Valdecoxib showed a significant increase compared to ibuprofen, naproxen and celecoxib (Odds Ratios 1.21, 1.16 and 1.06). Ibuprofen showed a significantly decreased risk relative to all medications except naproxen. Ninety-five percent confidence intervals are included in the full report.

When considering only cardiovascular risk, this study suggests prescribers should consider ibuprofen or naproxen as the primary agent of choice, with meloxicam, and celecoxib as reasonable second choices. Ultimately, the decision must also weigh the patient's risk of gastrointestinal side effects, cost of therapy and other individual considerations.

I. INTRODUCTION

A. BACKGROUND OF ANTI-INFLAMMATORY AGENTS

1. NSAID Actions

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective agents commonly used for the relief of both acute and chronic pain and inflammatory conditions. Though effective, life-threatening complications from use of traditional NSAIDs, i.e. ibuprofen and naproxen, such as gastrointestinal (GI) ulceration, hemorrhage and perforation, led to research and development of a sub-class of anti-inflammatory agents called cyclooxygenase-2 enzyme (COX-2) inhibitors. Cyclooxygenase-1 enzyme (COX-1) is thought to be a protective factor for the mucosal lining of the gastrointestinal tract and normal platelet function while COX-2 is believed to be primarily responsible for mediating the inflammatory response and its subsequent pain production. Since traditional NSAIDs produce relief by blocking both COX-1 and COX-2, it was felt that GI toxicities may be alleviated by producing agents that could selectively inhibit COX-2 (Cryer & Feldman, 1998). The ratios of selectivity and differences of traditional NSAIDs have previously been evaluated *ex vivo* (Cryer & Feldman, 1998) although *in vivo* studies have yet to clearly demonstrate the clinical significance of these differences.

2. COX-2 Selective and Preferential Agents

During pre-clinical testing of rofecoxib (Vioxx), it was noted that COX-2 was also produced in endothelial cells of blood vessels initiating concern over a potential for harmful cardiovascular effects if inhibited (Weir, Sperling, Reicin, & Gertz, 2003). This concern was not demonstrated to be of significance during initial clinical trials at doses of 25mg or less, and thus rofecoxib was brought to market (Bull & Seligman, 2005). However, concern over cardiac safety has plagued the COX-2 selective inhibitors since introduction to the market of rofecoxib and celecoxib (Celebrex) in 1999. A third agent, valdecoxib (Bextra) was added to the market in 2002. Nevertheless, the safety concern was placed in the background as these agents quickly took hold in the marketplace, resulting in an estimated total of 105 million prescriptions for rofecoxib alone in the United States from May 1999 through August 2004 (Merck, 2005). Investigators have

identified a third category of NSAIDs, containing the agents meloxicam (Mobic) and etodolac (Lodine). This third category is considered to be COX-2 preferential, but exhibits more blocking of COX-1 than the selective COX-2 inhibitors, positioning this third category of agents as intermediaries between the non-selective and selective therapies.

3. DoD Financial Impact of COX-2 Agents

Department of Defense (DoD) healthcare beneficiaries who received prescription benefits under the TRICARE program filled approximately 175,000 prescriptions for COX-2 agents alone in July of 2004, at a cost of more than \$7 million. Figures 1 and 2 (From Trice, 2005) indicate a breakdown of NSAID prescriptions filled under the TRICARE Military Health System (MHS), and their respective costs according to the method by which prescriptions were obtained. Of particular note are the steadily increasing overall NSAID costs in millions of dollars in Figure 2. These are primarily the result of introduction of COX-2 inhibitors as illustrated by the breakdown presented in Figure 3.

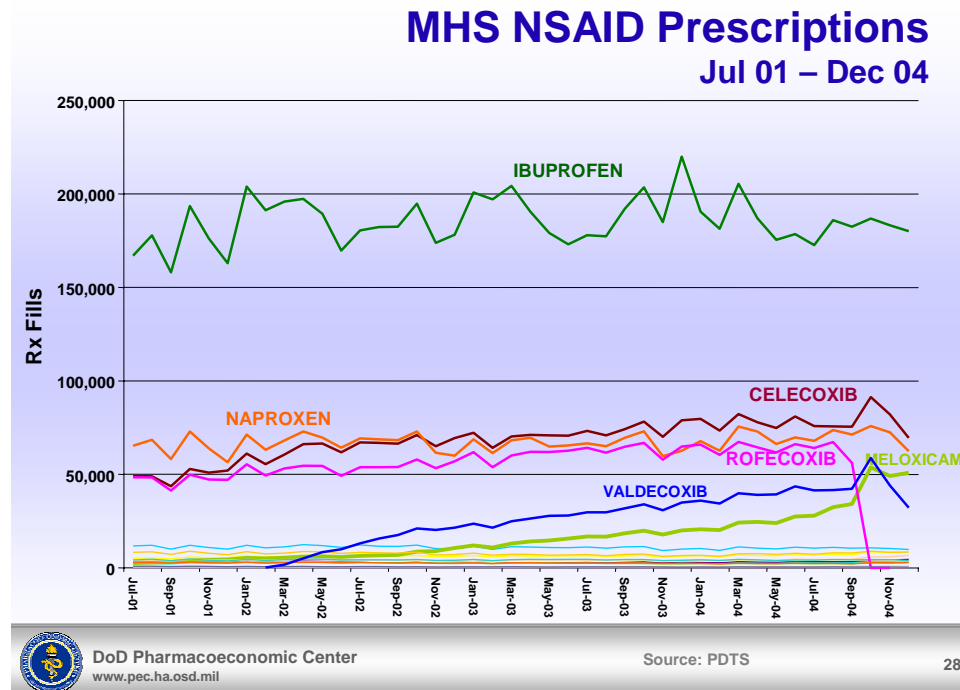


Figure 1. MHS NSAID Prescriptions Jul 01-Dec 04 (From Trice 2005)

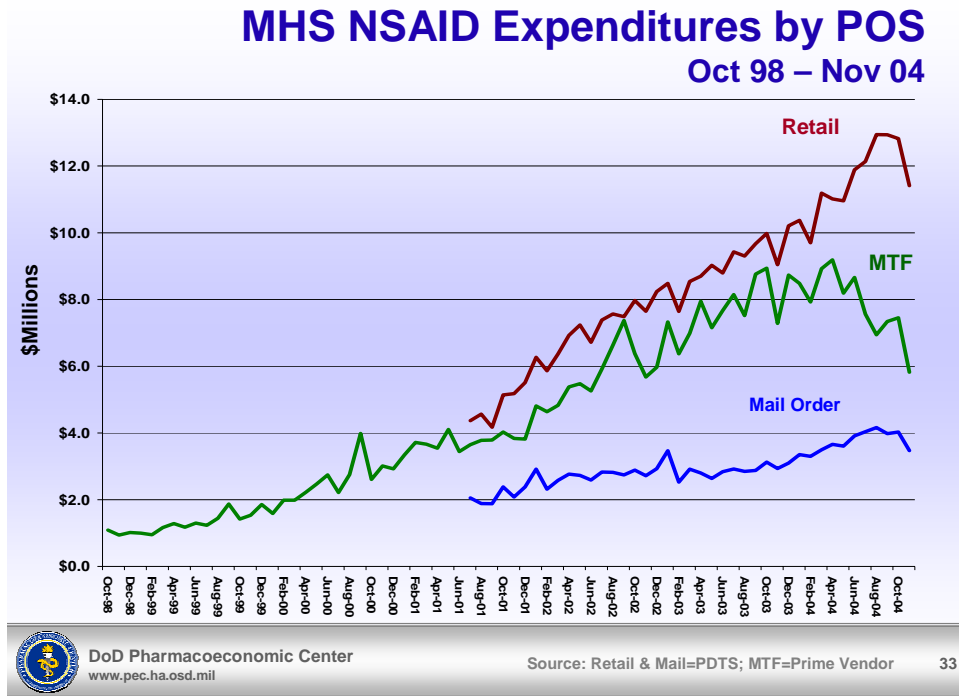


Figure 2. MHS NSAID Expenditures by Point of Service (From Trice 2005)

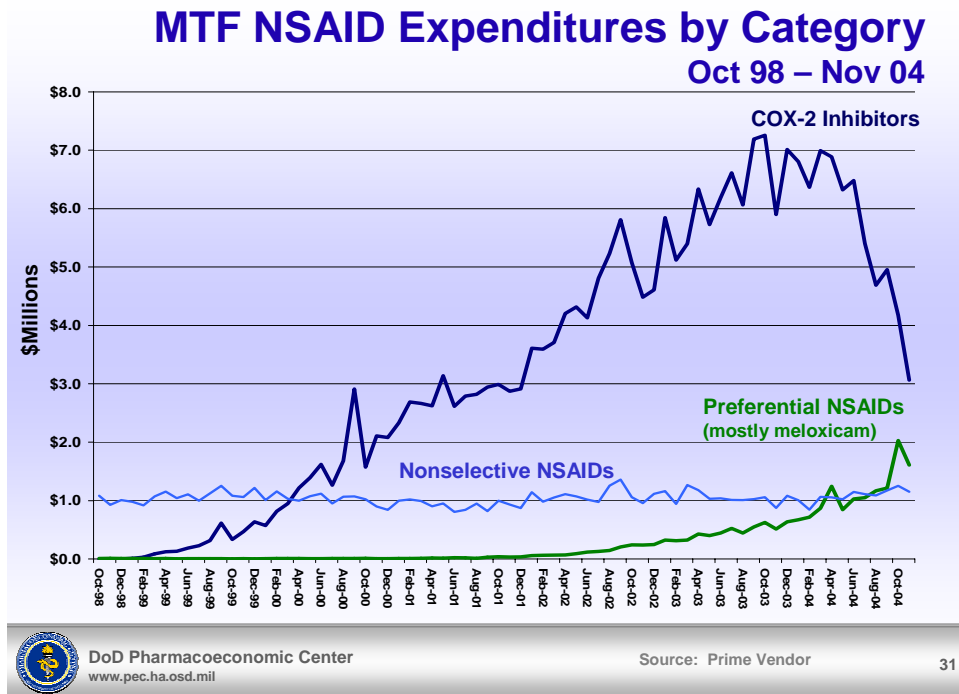


Figure 3. MTF NSAID Expenditures by Category (From Trice 2005)

Figure 3 depicts the dramatic increase in expenditures in military treatment facility (MTF) budgets due to COX-2 agents. It does not contain information from

prescriptions filled at TRICARE network pharmacies as Figures 1 and 2 do. On a positive note, as expected, COX-2 expenditures dropped significantly following market withdrawal of rofecoxib.

B. PROBLEM DESCRIPTION

1. Market Withdrawal of Vioxx and Bextra

On 30 September 2004, Merck & Co., Inc., announced voluntary withdrawal from the market of its popular drug rofecoxib due to mounting clinical evidence that it increased cardiovascular (CV) risk, that is, risk of stroke or myocardial infarction, when compared to placebo or to the risk among individuals not taking such an agent. Study investigators in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial reported preliminary findings that rofecoxib increased the risk for confirmed CV events twofold when compared with placebo, and halted the study early (Bull & Seligman, 2005; Lévesque, Brophy, & Zhang, 2005). The CV effects were not evident during the first 18 months of the APPROVe study and were only evident at the three-year data point (Merck, 2005). Previously, in 2000, Vioxx Gastro Intestinal Outcomes Research Trial (VIGOR) investigators reported a reduced risk of severe gastrointestinal toxicity with patients treated with rofecoxib, but a greater risk was found for CV thromboembolic events in rofecoxib patients versus those treated with naproxen (Bull & Seligman, 2005). This study was conducted using a rofecoxib dose of 50mg whereas previous studies using a dose of 25mg did not have similar findings. This resulted in a labeling change for Rofecoxib in April of 2002 indicating an increased risk of CV thromboembolic events at the 50mg dose, but marketing continued.

Voluntary withdrawal of rofecoxib following the preliminary results of the APPROVe trial prompted an in-depth review of the entire class by the Food and Drug Administration (FDA) amid concern of whether the other agents, celecoxib and valdecoxib, shared the same risks. Studies to date have produced conflicting results (Bull & Seligman, 2005; Levesque et al., 2005; Solomon et al., 2004). After significant debate, valdecoxib was found to have no advantages over rofecoxib and celecoxib, and possessed an increased incidence of a potentially life-threatening skin reaction. This resulted in an unfavorable overall benefit versus risk profile and subsequent FDA recommendation for

removal from the market (Appendix B). Valdecoxib was removed from the market as a result, leaving celecoxib as the sole COX-2 agent. Of significance, full recommendations from the FDA review also call into question the CV safety of non-selective NSAIDs (Appendix B).

2. DoD Impact

Withdrawal from the market of two out of three available COX-2 inhibitors and strengthened warnings on non-selective NSAIDs raises several questions with respect to prescribing habits within the DoD. First, for patients previously taking one of the now unavailable medications, what should they be switched to? Second, since the FDA was unable to rank the COX-2 inhibitors and other NSAIDs with respect to cardiovascular risk; does the TRICARE data provide evidence to suggest a ranking of medications in this category? Are the studies used by the FDA to evaluate cardiovascular risk of the COX-2 agents representative of the DoD population? How do the cardiovascular risk profiles of the COX-2 agents compare to those of the traditional NSAIDs or preferential agents? Given the volume of prescriptions and their associated expenditures, it is possible that millions of dollars may be saved by switching patients from rofecoxib or valdecoxib to the intermediate meloxicam, instead of the more costly celecoxib, without placing patients at an increased CV risk.

C. HOW THIS ANALYSIS SUPPORTS PROBLEM RESOLUTION

This study attempts to quantify cardiovascular risks of COX-2 selective agents specifically in the DoD TRICARE population when compared with traditional NSAIDs, ibuprofen and naproxen, as well as with the preferential COX-2 agent, meloxicam. The DoD prescription volume and cost data necessitate a thorough study of this issue to determine recommendations and guidance on how DoD physicians and patients should position further use of NSAIDs that remain on the market to minimize both cost and patient risk. The results produced in this report can be used in a complete cost-benefit analysis of the NSAID class. Additionally, there is a possibility that COX-2 agents in development will become available in the future. Hence, clarification of the factors associated with increased CV risk in this widely used class of medications is prudent. “Cardiovascular effects among the COX-2 inhibitors seem different, but further studies,

preferably randomized trials, are needed to fully understand the spectrum of effects of COX-2 inhibitors and potential differences among them.” (Lamb, 2004)

II. METHODS

A. STUDY POPULATION AND DATA SOURCE

This study was conducted as a retrospective record review of patients who took NSAIDs and experienced a CV event (stroke or MI) compared to those who took NSAIDs and did not experience an event. The population used for this study was all TRICARE beneficiaries of age 40 or greater (at the time of first prescription receipt) who received one or more prescriptions for the products of interest during the calendar years of 2002, 2003, 2004. Eligible beneficiaries included active duty members, dependents of active duty members, retirees and dependents of retirees. Data were obtained from the TRICARE M2 database, accessed by the DoD Pharmacoeconomic Center (PEC) in Fort Sam Houston, TX. A total of 1,523,357 patients were entered into the study. The following items were included in the database: patient ID numbers, patient beneficiary category, age, NSAID(s), strength, quantity, date medication was obtained, CV events, and their corresponding dates. CV events were specified as those with Internal Classification of Diseases Ninth Revision (ICD-9) codes for acute myocardial infarction and stroke in the primary diagnosis field (codes 410.xx and 430.xx-436.xx respectively). Patient ID numbers were mapped to a pseudo-ID number by the PEC in order to preserve patient privacy.

B. NSAID CATEGORIES

Popular medications from each of the three NSAID were selected for comparison. In the non-selective category, ibuprofen and naproxen were selected, since these were by far the most frequently prescribed and recent questions had arisen with regard to cardiovascular risks of both agents (Hippisley-Cox & Coupland, 2005; Graham et al., 2005). Meloxicam was chosen from the intermediate COX-2 preferential category and all three COX-2 specific agents, rofecoxib, celecoxib and valdecoxib, were studied. Each medication average daily dosage was defined as either high or low and the *a priori* designations are shown in Table 1. *A priori* determinations were established in accordance with those used in previous studies (Weir, Sperling, Reicin, & Gertz, 2003; Solomon et al., 2004).

Medication	Low Dose	High Dose
Rofecoxib	≤ 25 mg	>25 mg
Celecoxib	≤ 200 mg	>200 mg
Valdecoxib	≤ 20 mg	>20 mg
Meloxicam	≤ 15 mg	>15 mg
Ibuprofen	≤ 1800 mg	>1800 mg
Naproxen	≤ 1000 mg	>1000 mg

Table 1. Dosing designations

C. DATA MANAGEMENT

S-Plus 7.0 Enterprise Edition statistical software was used for all data management and analyses (Copyright (c) 1988, 2005 Insightful Corp.). Raw data was initially obtained in five separate files. The two event files contained patient ID's and information regarding hospital admissions for diagnoses of acute myocardial infarction or stroke. One event file contained information and dates from MTFs and the other contained similar information from TRICARE network civilian medical facilities. These files represented all incidents of acute myocardial infarction and stroke in the population without regard to NSAID status. These two event files were combined, and entries with missing ID numbers or other missing information were removed, as were those with events occurring prior to January 1, 2002, resulting in a total of 93,829 entries from the original 120,456. The other three files, containing prescription information for years 2002, 2003, and 2004, were merged into one file with a total of 7,955,610 records. After prescription entries with missing information or those prescriptions which were obtained following an event were removed the total number of prescription entries was 7,907,970. Entries for products that were listed by more than one name were edited so that all names for the same product were consistent. For example, ibuprofen was listed as Motrin, Motrin IB or ibuprofen, so all occurrences were changed to "Motrin." Average daily doses were calculated by multiplying the milligram strength of the product by the quantity received and dividing by the days supply. If there was more than one product obtained by an individual, this calculation was done for each product. The event file IDs were screened against the IDs in the prescription file to determine association of an event with that particular individual. This screening resulted in a reduction of entries in the

event file from 93,829 to 33,342 as those individuals having events who did not receive prescriptions for NSAIDs were removed. If the event was more than thirty days following the end of any prescription period as determined by days supply, the event was not associated with a prescription. Also, if there was more than one event for a particular individual, the first event was used so that there was no more than one event per person. When the ID number had more than one product listed, the event was associated with the prescription having the closest date to the event but not following. The final event file, consisting of those events considered to be associated with a particular prescription, contained 12,023 entries.

D. STATISTICAL ANALYSIS

Analysis was performed using a logistic regression model to estimate odds ratios with the response variable being event or no event. Differences in these ratios and their respective confidence intervals were calculated. Predictor variables and possible confounders were: age, medication, dose category, and beneficiary category. Each of the variables was treated as a categorical factor. The equation describing the model is:

$$\log\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta_1 age_i + \beta_3 med_i + \beta_4 dose_i + \beta_5 bencat_i$$

where p_i is the probability of an individual having a CV event and i goes from one to k , with k being the number of different combinations of factor levels; age is the age bin of the patient, med is the medication he or she was prescribed, $dose$ is the *a priori* high or low designation, and $bencat$ is the beneficiary category.

The age variable was classified into 12 bins, each spanning 5.5 years. Since the last 3 age bins contained less than 1 percent of the population, they were combined resulting in a total of 10 bins. The bins and percentages of patients in each bin are shown in Table 2. Age was determined by evaluating patient age as of the end of the study period.

Age Bins (yrs)		%
1	[41.28,46.78)	9.59
2	[46.78,52.27)	11.53
3	[52.27,57.77)	11.70
4	[57.77,63.26)	12.29
5	[63.26,68.75)	15.12
6	[68.75,74.25)	16.11
7	[74.25,79.74)	11.71
8	[79.74,85.23)	8.36
9	[85.23,90.73)	2.96
10	[90.73,107.21]	0.63

Table 2. Age Bins

Medication dosage classification is given in Table 1. The response variable, occurrence of a CV event, was coded as a “1,” while absence of an event was coded as a “0.” Beneficiary categories from the M2 database were used. The categories are listed in Table 3.

ACT	Active Duty
DA	Dependent of Active Duty
DGR	Dependent of Guard/Reserve
DR	Dependent of Retiree
DS	Survivor
GRD	Guard/Reserve
IGR	Inactive Guard/Reserve
OTH	Other
RET	Retiree
Z	Unknown

Table 3. Beneficiary Categories

III. RESULTS

A. DISTRIBUTION INFORMATION

1. Medication Distribution

Figure 4 indicates the distribution of prescriptions by product and dosing category. Celecoxib had the largest number of prescriptions dispensed at more than 2.23 million. Rofecoxib followed with more than 1.79 million prescriptions, valdecoxib had more than 0.7 million prescriptions, while ibuprofen, naproxen and meloxicam recorded 1.7, 1.02 and 0.41 million prescriptions respectively.

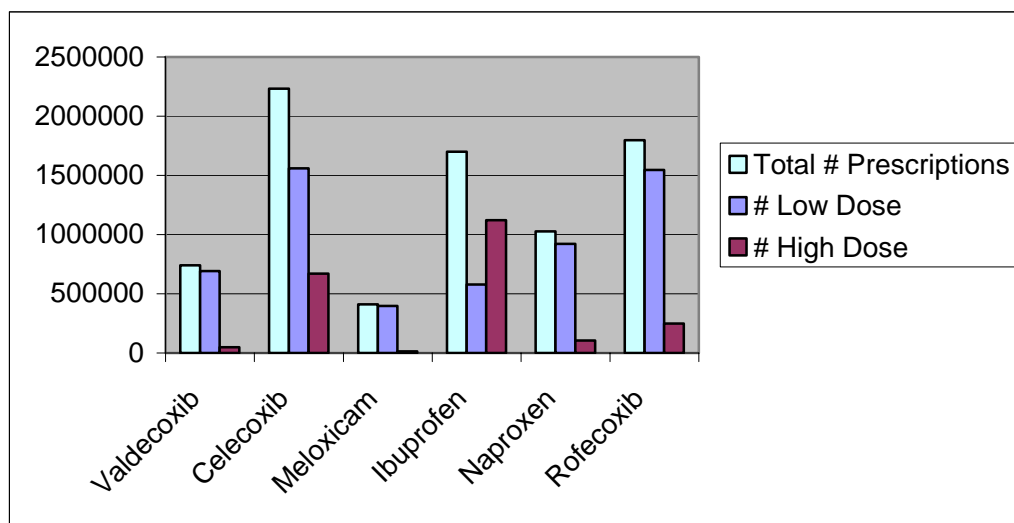


Figure 4. Number of Prescriptions by Product and Dosage

Of note, ibuprofen prescriptions were dispensed much more consistently at the upper limit of the dosing range than any of the other products. The result of categorizing prescriptions by both age and dose according to medication is presented in Appendix C. The percentage of COX-2 agents consistently increased with age, ranging from 29.3% for the youngest group to 84.5% for the oldest. The population age distribution is presented in Figure 5. The mean patient age was 64.4 years.

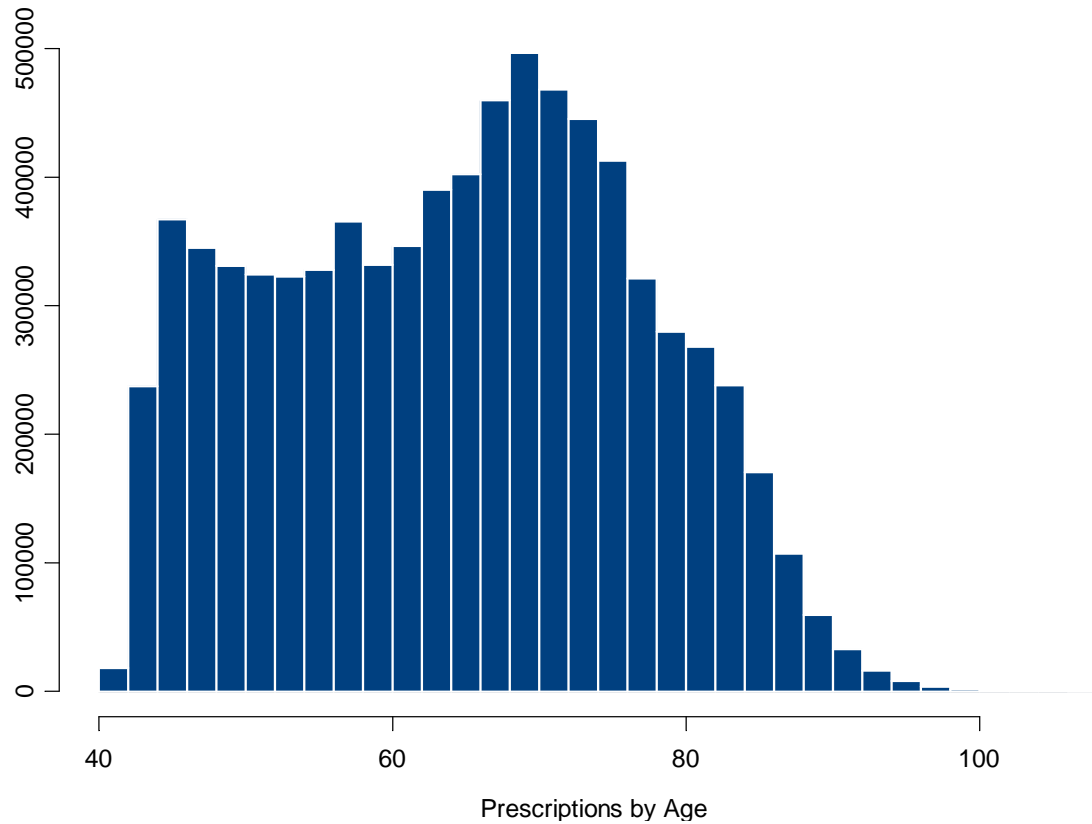


Figure 5. Age Distribution

2. Event Distribution

Raw event rates for each medication and age grouping are given in Figures 6 and 7 respectively. Raw event rates increase with age.

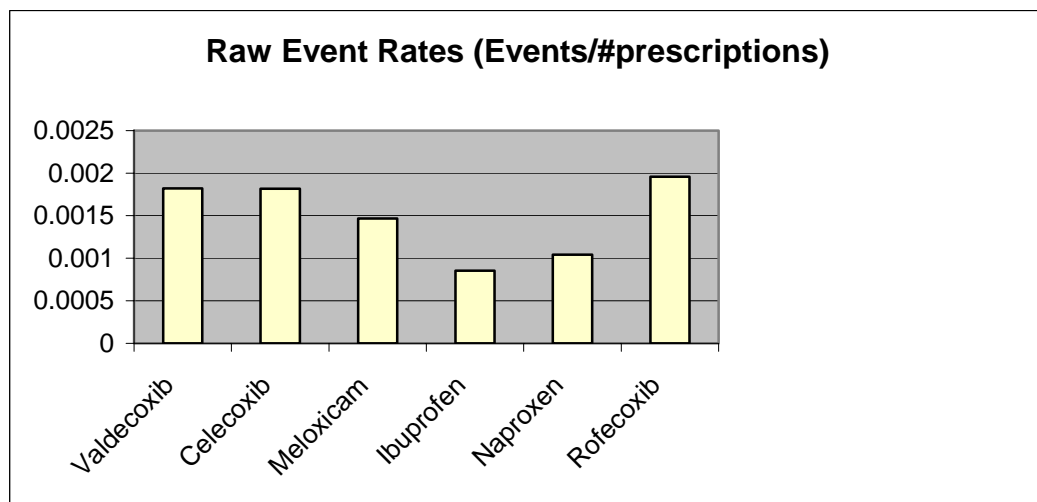


Figure 6. Events by Medication

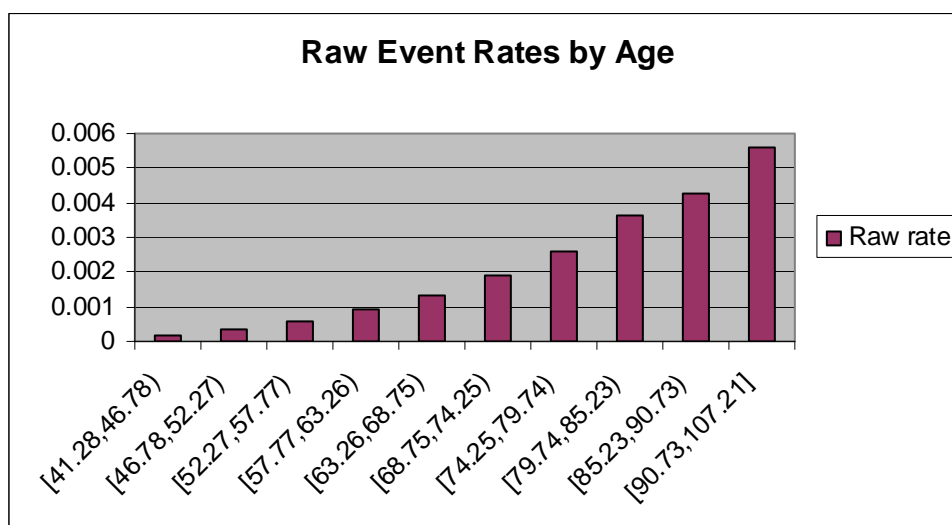


Figure 7. Events by Age

B. STATISTICAL RESULTS

The regression model resulted in a residual deviance of 172,742 with 7,907,969 total and 7,907,945 residual degrees of freedom. The full model and estimated coefficients are listed in Appendix D. A summary of the results of every pairwise comparison of products is given in Table 3. Odds ratios for comparisons to the base medication, valdecoxib, were calculated from the coefficients estimated in the model (see Appendix D). Confidence intervals for the comparisons were calculated using the standard errors for the coefficients estimated by the model. For comparisons not involving the base medication, differences in odds were calculated by subtraction of the corresponding estimated coefficients. Confidence intervals for these differences were based on standard errors computed from the standard errors of each estimated coefficient along with the appropriate correlation coefficient. Several statistically significant differences, marked by bold type in Table 4, were noted among the various agents in the study when compared for incidence of cardiovascular events.

Rofecoxib had a significantly higher risk than all other agents. Analysis shows increased odds of CV events by 23% and 28% for rofecoxib when compared to naproxen and ibuprofen respectively. The results suggest an overall ranking of increasing risk as follows: ibuprofen, naproxen, meloxicam, celecoxib, valdecoxib and rofecoxib with not

all differences being significant. Figure 8 depicts the statistical differences among the agents. Agents underscored by the same bar were not found to be statistically different. Note that although meloxicam was not found to be different from either celecoxib or valdecoxib, celecoxib and valdecoxib were found to be different from each other. This can be attributed to the difference in sample sizes. Meloxicam had fewer than 0.45 million prescriptions, celecoxib had greater than 2 million prescriptions and valdecoxib had greater than 0.7 million.

Ibuprofen Naproxen Meloxicam Celecoxib Valdecoxib Rofecoxib

Figure 8. Differences

Medication	OR	Lower Limit	Upper Limit
Celecoxib/Valdecoxib	0.936	0.879	0.997
Meloxicam/Valdecoxib	0.930	0.845	1.024
Ibuprofen/Valdecoxib	0.789	0.728	0.854
Naproxen/Valdecoxib	0.843	0.777	0.914
Rofecoxib/Valdecoxib	1.094	1.027	1.165
Celecoxib/Meloxicam	1.006	0.923	1.098
Celecoxib/Ibuprofen	1.187	1.115	1.264
Celecoxib/Naproxen	1.110	1.037	1.189
Celecoxib/Rofecoxib	0.855	0.811	0.890
Meloxicam/Ibuprofen	1.180	1.068	1.303
Meloxicam/Naproxen	1.103	0.998	1.220
Meloxicam/Rofecoxib	0.850	0.779	0.927
Ibuprofen/Naproxen	0.935	0.861	1.016
Ibuprofen/Rofecoxib	0.721	0.674	0.770
Naproxen/Rofecoxib	0.770	0.719	0.825

Table 4. NSAID Odds Ratios (OR) and 95% Confidence Intervals

IV. DISCUSSION

A. GENERAL DISCUSSION

This study, with 1,523,357 patients, is consistent with the conclusions of recent studies (Graham et al., 2005; Kimmel et al., 2005; Levesque et al., 2005) and a meta-analysis (Juni et al., 2004). Additionally, the data suggest that the conclusions of prior studies in elderly patients can indeed be extended to a younger population. These results also support the suggestion that naproxen may exhibit a cardioprotective effect (Juni et al., 2004) with respect to other NSAIDs but not to non-NSAID users). This suggestion was not supported by a previous observational study which did not evaluate dosing effects and found no evidence of increased risk for rofecoxib or any other NSAIDs (Mamdani et al., 2003). Also, a study of Medicare beneficiaries reported increased relative risk with rofecoxib when compared to celecoxib and use of no NSAIDs, but showed no other differences among the other comparisons (Solomon et al, 2004).

The majority of previous studies have been in elderly (age > 64) or otherwise limited populations (Levesque et al., 2005; Mamdani et al., 2003; Nussmeier et al., 2005; Solomon et al., 2004) although a few of the most recent have included patients as young as 40 and 18 years of age (Graham et al., 2005; Hippisley-Cox & Coupland, 2005; Kimmel et al., 2005). Additionally, the majority have studied only myocardial infarction as an endpoint. Reicin et al. (2002) studied a much broader group of endpoints including myocardial infarction, cerebrovascular accidents, and cardiovascular, hemorrhagic and unknown death, but rofecoxib was the only COX-2 agent available for study at the time. Unfortunately, dose differentiations and duration of treatment were not studied by Reicin, and the conclusion was that there were no differences in risk of events among medications studied. These earlier results have since been studied further and the dosing risks and length of exposure risks with rofecoxib have become clearer (Bull & Seligman, 2005). The preferentially selective agent meloxicam, which few previous studies have considered, was included in this current report (Garcia Rodriguez, Varas-Lorenzo, Maguire, Gonzalez-Perez, 2004; Levesque et al., 2005). Garcia Rodriguez et al. (2004) compared a variety of non-selective NSAIDs as well as meloxicam and found no

difference among any of the agents and risk of MI. The present study did find a difference between meloxicam and ibuprofen.

Hippisley-Cox and Coupland (2005) reported an increased risk of MI for ibuprofen when compared to naproxen, a result which is not supported by the present study. Cryer and Feldman (1998) determined *ex vivo* that ibuprofen was more selective for COX-1 than naproxen and that naproxen was more selective for COX-2, so the previously reported increased risk for ibuprofen remains unexplained and unsupported.

Although gaining a clearer understanding of the risk differences among COX-2 inhibitors and non-selective NSAIDs may seem to be a moot point since only celecoxib remains on the market, development of other anti-inflammatory agents with a reduced risk of gastrointestinal side effects is still a desirable goal; thus an improved understanding is indeed helpful.

B. PROBLEMS AND LIMITATIONS

1. Age Restriction

The population age was restricted to individuals of age 40 or above due to the abundance of NSAID prescriptions for acute conditions and relatively minimal incidence of cardiovascular events in younger individuals. This restriction allowed for study of the entire TRICARE population of age greater than or equal to 40. Inclusion of younger patients would have been computationally prohibitive or required a change to a random sample or case-control design. Increased risk of MI with rofecoxib at doses of greater than 25 mg/day has previously been established in patients as young as 18 (Graham et al., 2005; Levesque et al., 2005). Another recently published article supported an increased risk of MI among patients of ages 25 and above taking rofecoxib, ibuprofen or diclofenac, versus patients not taking those drugs, but did not elucidate any dosage differences (Hippisley-Cox & Coupland, 2005).

Patient age was calculated for all patients using the date at the end of the study period. Thus, a patient of age 41 entering the study and experiencing an event in 2002 would be recorded as age 43, while a 41 year old patient entering in 2004 would be recorded as 41. Using the date of birth to calculate an age at the time of each prescription

issue may have been a more appropriate calculation and allowed for natural age progression throughout the study period.

Partitioning of age into bins was performed *a priori* without benefit of a tree or partitioning function. The size of the data precluded use of either of these methods of categorization though their use could have improved the model.

2. Confounders

This study could not account for all confounders. Access to data was limited and a simple study design was desired. However, it is likely that beneficiary category acted as a surrogate for some of the potential confounders that were not included. For instance, active duty service members are generally healthier than individuals not serving on active duty. When significance of the variable beneficiary category was tested by running the model without that variable, a p-value of essentially zero indicated that the model including the variable was preferred. The residual deviance difference was 501 with a difference of 9 degrees of freedom.

Gender was only available in the event file and not in the prescription file, so this potential effect was not available for inclusion. Interestingly, this study achieved results similar to other studies with more complex designs intended to account for as many confounders as possible (Graham et al., 2005; Hippisley-Cox & Coupland, 2005; Solomon et al., 2004). Although Graham et al. (2005) found increased risk of MI with rofecoxib, they did not find a decreased risk with naproxen or ibuprofen (with respect to non-NSAID users) nor did Hippisley-Cox & Coupland (2005). Co-morbid conditions and medications, both prescription and over-the-counter (OTC), were not considered in this analysis, nor were smoking status, obesity, race, family history, physical activity or socioeconomic status. This may have introduced bias to the results since theoretically patients taking COX-2 inhibitors were at a higher risk of GI bleeding complications and thus in generally poorer health. This effect was possibly mitigated somewhat by taking age and beneficiary category into consideration. Also, one report found that confounding by smoking and aspirin use is “unlikely to materially alter estimates of associations between MI and use of prescription NSAIDs” (Velentgas, Cali, Diedrick, Heinen, et al., 2001).

a. *Aspirin and Other OTCs*

Additionally, concurrent use of aspirin which may decrease patient risk was not considered. Aspirin has been found to modify the risk of MI associated with the current use of rofecoxib at low doses, by eliminating the excess risk (versus patients not taking rofecoxib), but aspirin was found not to reduce the excess risk in patients taking rofecoxib at high doses (Levesque et al., 2005). Aspirin was found not to modify the risks associated with traditional NSAIDs or celecoxib and the association with meloxicam was indeterminate (Garcia Rodriguez et al., 2004; Levesque et al., 2005). Even in studies that do try to account for concurrent medication use, the possibility exists that over-the counter (OTC) medication use has not been accurately captured and remains unaccounted for. It was not expected that OTC medication use would be different across the different NSAID study medications, and Velentgas et al. (2001) support this conclusion.

b. *Socioeconomic Factors*

Information on potential confounding factors such as obesity, family history, physical activity, smoking status and socioeconomic status was not available, which may have introduced bias if there was an uneven distribution of these factors across the various medications. “Several studies have evaluated the potential for and magnitude of such bias and have demonstrated that any resulting bias would be negligible and directed toward the null.” (Levesque et al., 2005, p488) Hence a decision was made not to consider these other factors, and to assume that the socioeconomic status of patients taking anti-inflammatory agents was evenly distributed among the different agents.

c. *Co-morbid Conditions and Indications*

Studies that have accounted for co-morbidity have reported findings consistent with this report (Graham et al., 2005; Hippisley-Cox & Coupland, 2005; Levesque et al., 2005). Graham et al., (2005) calculated cardiovascular risk scores based on a regression of a multitude of factors, including cardiovascular admissions, emergency room visits for cardiovascular reasons, outpatient diagnoses for tobacco use, cardiovascular prescription drug use, arthritis, and hormone replacement therapy. Extensive data on co-morbidity was not available for inclusion in this analysis. It is also

thought that by comparing various NSAID users amongst themselves instead of to non-users, confounding by indication may be reduced (Juni et al., 2004).

d. Intermittent Use

The results are potentially confounded by the intermittent nature of use of this class of medications. Also, patients taking NSAIDs tend to try several different agents to find what they prefer best (Levesque et al., 2005). A thirty-day grace period was used in an attempt to account for this effect, but for those patients with multiple prescriptions, there is no way of actually knowing what was or was not being taken at the time of the event. The assumption was made that the most recently acquired prescription was likely being taken at the time of the event. Other studies differ in their classification of current or previous use and the classifications for use in this study are intermediate (Graham et al., 2005; Hippisley-Cox & Coupland, 2005; Kimmel et al., 2005; Levesque et al., 2005). Also, the dosage calculations are based on physician directions and quantities ordered, which are not necessarily consistent with how the patient actually took the medication.

3. Event Selection

It was assumed that the earliest recorded event date was the first occurrence of the event. All patients with an event date earlier than January 1, 2002 were discarded. This may not have been the case in reality. It is possible, though not likely, that the patient had an initial event that was not recorded in the TRICARE system and the current event was not actually the first. Another issue was the fact that patients could be admitted to the nearest civilian medical facility and then subsequently transferred to a military facility for further care. This would possibly show up as two separate events when it is indeed only one. This too supported use of the earliest event date. A second issue with coding is that all strokes were considered as events and they were not differentiated by classification as hemorrhagic versus ischemic. Ischemic events would be expected in the COX-2 medications while due to the antiplatelet activity of naproxen, hemorrhagic strokes could have been more likely.

Validity of use of the ICD-9, 410, in the primary diagnosis field for determination of MI's as an event has previously been established at positive predictive values of 92%

and 95% although these results may not be representative of the particular database used in this study (Graham et al., 2005; Levesque et al., 2005). Evidence was not found as to the validity of the ICD-9 classifications of stroke. It was assumed that the diagnoses were reasonably accurate and there were no differences in accuracy among the patients using the different medications.

4. Data Issues

a. ID Mapping

In order to preserve patient privacy and identities, the ID numbers were mapped and encoded to pseudoID's. The M2 database recorded information according to the patient's social security number prior to June 2003 and then used a Defense Enrollment Eligibility Reporting System (DEERS) number following that date to record information. Mapping both the social security and the DEERS enrollment number to one presented some difficulties in that not all would match properly, resulting in loss of 26,627 potential event records.

b. Size of Data

The two main data files containing the prescription information and event information were more than 800 megabytes, presenting issues with data management and statistical analysis. S-Plus 7.0 was used to process the data with functionality found in the BD Library. The BD Library was in an early stage of release and the commands in the BD Library did not always match up with or provide the same functionality as standard commands and functions.

A more thorough analysis that attempted to better account for confounders could have been attempted, but this would have required more or less continual access to the M2 database and extensive effort on the part of PEC personnel who were gracious enough to pull the requested data. Data size was also prohibitive for the use of partitioning functions in order to determine age bins or dosing categorization more efficiently. Addition of interaction terms also proved to be computationally prohibitive.

c. Data Integrity

Assessment of the distribution of patients in beneficiary categories and age bins provided evidence of misclassifications. Age category analysis indicated that there

were 2 patients over the age of 115 and that they were taking ibuprofen at the maximum dosage. These individuals were removed from the study, since the data was presumed to be inaccurate. It is possible and even likely that inaccuracy of birth dates led to more misclassifications of age, particularly in the last two age bins, but these instances could not be readily detected, were assumed to be a small percentage (less than 5%), and were not expected to favor any particular medication. There was also evidence of misclassification of beneficiary categories since it is highly unlikely that an individual of age greater than 90 years is serving on active duty. These individuals were left in the study for the same reasons as mentioned above.

Tamblyn, Lavoie, Petrella and Monette (1995) conducted an investigation into the accuracy of pharmacy claims databases utilized in pharmacoepidemiological research such as this. It was determined that the prescription claims database was an accurate means of determining drugs dispensed to individuals and also indicated that use of dosing information may have limitations. Although the database that was assessed was the prescription claims database in Quebec, it is reasonable to believe that the M2 database possesses similar accuracy.

C. COMPARATIVE STUDIES

While the results in this study support some of the more recent findings where rofecoxib has been clearly established as having an increased risk of MI (Graham et al., 2005; Levesque et al., 2005; Solomon et al., 2004), other fairly recent studies are not supported (Mamdani et al., 2003; Reicin et al., 2002). Reicin et al. (2002) lacked power to detect differences due to small sample sizes, a short study period (average 3.5 months), and a population limited to patients with osteoarthritis. Mamdani et al., (2003) used a Cox proportional hazards model, had large sample sizes, and accounted for multiple confounders. However, neither of these two studies categorized dosing into high or low ranges or attempted to quantify exposure. Most studies seem to be limited by different aspects; age of patients, post-surgery, concomitant use of aspirin, dose and stratification of medication use and limited selection of medication comparisons. While some studies report no increased incidence of MI's with COX-2's or NSAID's when compared to non-users, they do detect a difference in risks with rofecoxib consistently having the highest

risk (Hippisley-Cox & Coupland, 2005; Kimmel et al., 2005). The earlier conflicting studies were summarized in a meta-analysis by Juni et al. (2004) in an attempt to provide some clarification of results, but this analysis itself is not without criticism (Horton, 2004). Juni et al. (2004) found that rofecoxib had a relative risk of 2.24 (95% CI 1.24-4.02) when compared with control groups, and found that the relative risk for naproxen was 0.86 (95% CI 0.75-0.99). The meta-analysis included 20,742 patients who experienced a total of 52 MIs. Issues with the meta-analysis include the pooling of data from studies with 3 different kinds of comparators and the selective use of available data (Horton, 2004).

V. CONCLUSION AND RECOMMENDATIONS

This study provides information for prescribing NSAIDs as safely as possible when considering cardiovascular risk. It does not provide an evaluation of gastrointestinal risk which also must also be considered by patients and prescribers. This information may be used as part of a complete cost-benefit analysis for the remaining agents in the NSAID category. It supports the removal of both rofecoxib and valdecoxib from the market and provides direct comparisons of the remaining agents. The data suggests ibuprofen and naproxen are the NSAIDs of choice when considering CV events, with a ranking of increasing risk as follows: ibuprofen, naproxen, meloxicam and celecoxib. The difference between meloxicam and naproxen was not significant although the difference between meloxicam and ibuprofen was. Also, meloxicam was found not to be different from both celecoxib and valdecoxib although celecoxib and valdecoxib were different from each other.

The postulated theory that CV risk is a function of COX-2 inhibitory potency is also supported by these results (Levesque et al., 2005). Celecoxib and meloxicam have been shown to possess one tenth the COX-2 inhibition potency of rofecoxib and this is likely the reason for significantly different CV risks. It is possible that not differentiating between hemorrhagic versus ischemic strokes may have introduced bias to the naproxen group, since previous studies do suggest an increased CV risk with ibuprofen when compared to naproxen (Graham et al., 2005; Hippisley-Cox & Coupland, 2005). However, if the hemorrhagic events had been excluded, naproxen risk comparisons could only have improved.

Although this study has weaknesses with respect to confounders, it provides a good basis for further investigation into the differences and relative risks of the NSAIDs commonly prescribed. Classification of exposure into present users, recent users and previous users, or categorizing duration of use may have provided additional information not captured in the study model. Additional information may also have been gained by accounting for prescribing indications, co-morbid disease states, and gender. This information was not available for this study as access to the database was somewhat

limited. Follow-up studies with this additional information may be helpful in providing further distinctions among this class of medications. Also, a comparison of patients who did not take NSAIDs by adding a matched control group would provide additional information.

It is interesting that this simple study design provided results which are generally consistent with recent large observational studies that accounted extensively for potential confounders (Graham et al., 2005; Hippisley-Cox & Coupland, 2005; Kimmel et al., 2005; Levesque et al., 2005). The beneficiary category variable may have acted as a surrogate for other potential confounders.

While this report assumed reasonable accuracy of the database with respect to quantities and dosing of patients, an investigation of data integrity of the M2 database, such as that by Tamblyn et al. (1995), would be helpful.

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APPENDIX A. LIST OF ACRONYMS

COX- cyclo-oxygenase enzyme

CV- cardiovascular

DEERS- defense eligibility enrollment system

FDA-Food and Drug Administration

GI- gastrointestinal

M2-DoD TRICARE healthcare database

MHS- military health system

MI- myocardial infarction

MTF- military treatment facility

NSAID- non-steroidal anti-inflammatory agent

OTC- over-the-counter

PEC- Pharmacoeconomic Center

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APPENDIX B. FDA DECISION MEMORANDUM

MEMORANDUM

DATE: April 6, 2005

FROM: John K. Jenkins, M.D.

Director, Office of New Drugs (OND)

and

Paul J. Seligman, M.D., M.P.H.

Director, Office of Pharmacoeconomics and Statistical
Science (OPaSS)

THROUGH: Steven Galson, M.D., M.P.H.

Acting Director, Center for Drug Evaluation and Research

TO: NDA files 20-998, 21-156, 21-341, 21-042

SUBJECT: Analysis and recommendations for Agency action regarding non-steroidal anti-inflammatory drugs and cardiovascular risk

Executive Summary

Following a thorough review of the available data we have reached the following conclusions regarding currently approved COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs)¹ and the risk of adverse cardiovascular (CV) events:²

- The three approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib, and valdecoxib) are associated with an increased risk of serious adverse CV events compared to placebo. The available data do not permit a rank ordering of these drugs with regard to CV risk.
- Data from large long-term controlled clinical trials that have included a comparison of COX-2 selective and non-selective NSAIDs do not clearly demonstrate that the COX-2 selective agents confer a greater risk of serious adverse CV events than non-selective NSAIDs.
- Long-term placebo-controlled clinical trial data are not available to adequately assess the potential for the non-selective NSAIDs to increase the risk of serious adverse CV events.
- Pending the availability of additional long-term controlled clinical trial data, the available data are best interpreted as being consistent with a class effect of an increased risk of serious adverse CV events for COX-2 selective and non-selective NSAIDs.

¹ A list of the non-selective NSAIDs is available on
<http://www.fda.gov/cder/drug/infopage/cox2/default.htm>.

² The degree of COX-2 selectivity for any given drug has not been definitively established, and there is considerable overlap in *in-vitro* COX-2 selectivity between agents that have been generally considered to be COX-2 selective (e.g., celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, etoricoxib) and older NSAIDs that have been considered to be non-selective (e.g., diclofenac, ibuprofen, naproxen). For purposes of simplicity of discussion and comparisons, this document maintains the traditional separation between COX-2 selective and non-selective agents, but our use of this nomenclature should not be considered as FDA endorsement of such designations.

- Short-term use of NSAIDs to relieve acute pain, particularly at low doses, does not appear to confer an increased risk of serious adverse CV events (with the exception of valdecoxib in hospitalized patients immediately post-operative from coronary artery bypass (CABG) surgery).

- Controlled clinical trial data are not available to rigorously evaluate whether certain patients derive greater relief of pain and inflammation from specific NSAIDs compared to others or after failing to respond to other NSAIDs.
- The three approved COX-2 selective drugs reduce the incidence of GI ulcers visualized at endoscopy compared to certain non-selective NSAIDs. Only rofecoxib has been shown to reduce the risk of serious GI bleeding compared to a non-selective NSAID (naproxen) following chronic use. The overall benefit of COX-2 selective drugs in reducing the risk of serious GI bleeding remains uncertain, as does the comparative effectiveness of COX-2 selective NSAIDs and other strategies for reducing the risk of GI bleeding following chronic NSAID use (e.g., concomitant use of a non-selective NSAID and a proton pump inhibitor).
- Valdecoxib is associated with an increased rate of serious and potentially life-threatening skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) compared to other COX-2 selective agents and is the only NSAID with a boxed warning for this adverse event in its approved package insert. In the absence of any demonstrated advantage over other NSAIDs, the overall benefit versus risk profile for valdecoxib is unfavorable for marketing.

Based on these conclusions, we recommend the following regulatory actions to further improve the safe and effective use of these drugs by prescribers, patients, and consumers: change footer to 1” – check all the way through

- The agency should ask Pfizer to voluntarily withdraw Bextra (valdecoxib) from the U.S. market. In the event Pfizer does not agree to a voluntary withdrawal, the agency should initiate the formal withdrawal procedures; i.e., issuance of a Notice of Opportunity for Hearing (NOOH).
- The professional labeling for all prescription NSAIDs should be revised to include a boxed warning highlighting the potential increased risk of serious adverse CV events. The boxed warning should also include the well described NSAID class risk of serious, and often life-threatening, GI bleeding, which is currently contained in a bolded warning.
- Pending the availability of additional data, the labeling for all prescription NSAIDs should include a contraindication for use in patients immediately post-operative from CABG surgery.
- A class NSAID Medication Guide should be developed to inform patients of the potential increased risk of serious adverse CV events and the risk of serious GI bleeding.
- The labeling for non-prescription NSAIDs should be revised to include more specific information about potential CV and GI risks and information to assist consumers in the safe use of these drugs.
- The boxed warning for Celebrex (celecoxib) should specifically reference the available data that demonstrate an increased risk of serious adverse CV events and other sections of the labeling should be revised to clearly reflect these data.

- The agency should carefully review any proposal from Merck for resumption of marketing of Vioxx (rofecoxib). We recommend that such a proposal be reviewed by the FDA Drug Safety Oversight Board and an advisory committee before a final decision is reached.
- The agency should request that all sponsors of non-selective NSAIDs conduct and submit for FDA review a comprehensive review and analysis of available controlled clinical trial databases to further evaluate the potential for increased CV risk.
- The agency should work closely with sponsors and other interested stakeholders (e.g., NIH) to encourage additional long-term controlled clinical trials of non-selective NSAIDs to further evaluate the potential for increased CV risk.

Background

Vioxx (rofecoxib) was voluntarily withdrawn from the market by Merck in September 2004 following the observation of an increased risk of serious adverse CV events compared to placebo in a long-term controlled clinical trial. Subsequent to that action, reports of additional data from controlled clinical trials became available for other COX-2 selective NSAIDs that also demonstrated an increased risk of serious adverse CV events compared to placebo. These new data prompted the agency to conduct a comprehensive review of the available data and to present the issue for review at a joint meeting of FDA's Arthritis and Drug Safety and Risk Management Advisory Committees on February 16-18, 2005.

Following the joint meeting, CDER conducted a thorough internal review of the available data regarding cardiovascular (CV) safety issues for COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This memorandum summarizes the major issues considered in that review, our conclusions regarding the interpretation of the available data, and our recommendations for regulatory actions necessary to further improve the safe and effective use of these drugs by prescribers, patients, and consumers.

Participants in the CDER review included staff from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, the Division of Over-the-Counter Drug Products, the Offices of Drug Evaluation II and V, the Office of New Drugs, the Office of Drug Safety, the Office of Biostatistics, the Office of Pharmacoeconomics and Statistical Science, the Office of Medical Policy, the Office of Regulatory Policy, and the Office of the Center Director. Materials reviewed included the regulatory histories and the NDA and postmarketing databases of the various NSAIDs, FDA and sponsor background documents prepared for the Advisory Committee meeting, all materials and data submitted by other stakeholders to the Advisory Committee meeting, presentations made at the Advisory Committee meeting, the discussions held by the Committee members during the meeting, and the specific votes and recommendations made by the joint Committee.

Summary of available data

The most persuasive evidence in support of an increased risk of serious adverse CV effects of the COX-2 selective NSAIDs is derived from a small number of long-term placebo- and active-controlled clinical trials in patients with arthritis or in the disease prevention setting. We will briefly summarize the available data from the long-term

controlled clinical trials for the three approved and two investigational COX-2 selective agents. We will also briefly summarize the available data from long-term controlled clinical trials to assess the potential for increased CV risk for the non-selective NSAIDs. Finally, we will briefly summarize the available data from observational studies that have sought to assess the potential for increased CV risk for NSAIDs. We will focus our discussion on the combined endpoint of death from CV causes, myocardial infarction (MI), and stroke, as that is a widely accepted endpoint in assessing the benefits and risks of a drug for CV outcomes. It should be noted that the exact definitions and adjudication procedures for this combined endpoint vary to some degree across the trials discussed below.

Celecoxib

The strongest data in support of an increased risk of serious adverse CV events for celecoxib comes from the National Cancer Institute's Adenoma Prevention with Celecoxib (APC) trial in patients at risk for recurrent colon polyps. In the APC trial a 2-3 fold increased risk of adverse CV events was seen for celecoxib compared to placebo after a mean duration of treatment of 33 months. There was evidence of a dose response relationship, with a hazard ratio³ of 2.5 for celecoxib 200 mg twice daily and 3.4 for celecoxib 400 mg twice daily compared to placebo for the composite endpoint of death from CV causes, myocardial infarction (MI), or stroke.

The results from the APC trial were not replicated, however, in the nearly identical Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial. Based on preliminary, unpublished data presented by the PreSAP investigators at the AC meeting, the hazard ratio was 1.1 for celecoxib 400 mg once daily compared to placebo for the composite endpoint of death from CV causes, MI, or stroke. It is worth noting that the dosing interval differed between the APC trial (twice daily) and the PreSAP trial (once daily), although both trials included a total daily dose of celecoxib of 400 mg. It remains unclear what, if any, role this difference in dosing interval may have played in the disparate findings between the two trials.

Another long-term controlled clinical trial of celecoxib versus placebo, the National Institute of Aging's Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) in patients at risk for Alzheimer's disease, also does not appear to have shown an increased risk for celecoxib 200 mg twice daily compared to placebo for the composite endpoint of death, MI, or stroke. Preliminary, unpublished data shared with FDA by the ADAPT investigators showed no increased relative risk for celecoxib compared to placebo.⁴ Finally, there was a small one-year trial comparing celecoxib 200 mg twice daily to placebo in patients with Alzheimer's disease that did not demonstrate a significantly increased risk of serious adverse CV events, but did show a trend toward more CV events in the celecoxib treatment arm.

³ The hazard rate is a measure of risk per unit of time in an exposed cohort (e.g., the event rate per month). The hazard ratio is the ratio of the hazard rates from the treatment group relative to the control group, and is often used to represent the relative risk when the relative risk is constant over time.
Is this a footnote??

The only available data from a long-term comparison of celecoxib to non-selective NSAIDs come from the Celebrex Long-Term Arthritis Safety Study (CLASS) in which celecoxib 400 mg twice daily was compared to diclofenac and ibuprofen in approximately 8000 patients with osteoarthritis or rheumatoid arthritis. No differences were observed for serious adverse CV events between celecoxib and the two non-selective NSAID comparators in this trial.

The ADAPT trial also included naproxen as an active control and will provide an additional comparison of celecoxib to a non-selective NSAID when the final study results become available. Preliminary, unpublished data shared with FDA by the ADAPT investigators showed that celecoxib was intermediate between placebo (lowest incidence) and naproxen (highest incidence) for the composite endpoint of death, MI, or stroke.

Rofecoxib

The strongest data from a long-term placebo-controlled trial for an increased risk of serious adverse CV events with rofecoxib come from the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial in which rofecoxib 25 mg once daily was compared to placebo for up to three years. A relative risk of approximately two was seen for rofecoxib compared to placebo for serious adverse CV events. It is noteworthy that the rofecoxib and placebo CV event curves in a Kaplan-Meier plot did not appear to begin to separate until after approximately 18 months of treatment. In contrast to the results seen in APPROVe, two long-term placebo-controlled trials in patients with early Alzheimer's disease, including up to four years of treatment in a small number of patients, did not show a significant difference in CV events between rofecoxib 25 mg once daily and placebo.

The only long-term controlled clinical trial comparison of rofecoxib to a non-selective NSAID comes from the Vioxx GI Outcomes Research (VIGOR) trial in which rofecoxib 50 mg once daily was compared to naproxen for up to 12 months. In VIGOR, rofecoxib was associated with a hazard ratio of approximately two compared to naproxen based on the composite endpoint of death, MI, or stroke. In contrast to the findings in APPROVe, in VIGOR the Kaplan-Meier CV event curves for rofecoxib and naproxen began to separate after approximately two months of treatment.

⁴ Relative risk is defined as the cumulative risk in the treatment group (e.g., number of events per the number of individuals in this group) divided by the cumulative risk in the control group. The term relative risk is often used interchangeably with the hazard ratio. Footnote? Check all the way through

Valdecoxib

No long-term controlled clinical trials have been conducted comparing valdecoxib to either placebo or non-selective NSAIDs. Data are available from two short-term placebo-controlled trials of early dosing with intravenous parecoxib (a pro-drug for valdecoxib) followed by oral valdecoxib in patients immediately post-operative from coronary artery bypass graft (CABG) surgery. In both studies, valdecoxib was associated with an approximately two-fold increased risk of serious adverse CV events compared to placebo. In contrast, a short-term placebo-controlled trial of intravenous parecoxib followed by oral valdecoxib in patients undergoing various types of non-vascular general surgical procedures showed no differences for serious adverse CV events.

Investigational COX-2 Selective Agents

Data from long-term controlled clinical trials are also available for two investigational COX-2 selective agents (lumiracoxib and etoricoxib), and were presented at the AC meeting. These data are summarized here as they provide further insights regarding the issue of CV risk for COX-2 selective agents and the comparison of CV risks between COX-2 selective drugs and non-selective NSAIDs.

The Therapeutic COX-189 Arthritis Research and Gastrointestinal Event Trial (TARGET) compared lumiracoxib 400 mg once daily to naproxen and ibuprofen for one year in approximately 18,000 patients with osteoarthritis. TARGET was designed as two sub-studies and the planned primary analysis was to be the combined lumiracoxib groups compared to the combined naproxen and ibuprofen groups. The study design, however, did not clearly reflect this intent since randomization occurred at the sub-study level rather than across the entire study. For reasons that are not entirely clear, but possibly related in part to the randomization schema, the event rates for serious adverse CV events in the lumiracoxib groups in the two sub-studies were very different, i.e., 1.1 events per 100 patient years in the naproxen sub-study versus 0.58 events per 100 patient years in the ibuprofen sub-study. The event rates for serious adverse CV events for naproxen and ibuprofen were very similar in the two sub-studies; i.e., 0.76 events per 100 patient years for naproxen and 0.74 events per 100 patient years for ibuprofen.

The pre-specified primary analysis of TARGET found no difference in serious adverse CV events between the combined lumiracoxib groups and the combined naproxen and ibuprofen groups. The validity of combining the two lumiracoxib groups for purposes of the primary analysis is debatable, however, given the study design and the very different lumiracoxib event rates in the two sub-studies. It is unfortunate that the study design did not call for randomization of treatment assignment across the entire study, which would have allowed for a much more powerful comparison of lumiracoxib to the two non-selective NSAIDs.

Given the study design, the data from TARGET have also been analyzed by sub-study. In the naproxen sub-study, a hazard ratio of 1.44 was observed for the comparison of lumiracoxib and naproxen for serious adverse CV events. In the ibuprofen sub-study, a hazard ratio of 0.79 was observed for the comparison of lumiracoxib and ibuprofen for serious adverse CV events. The observed differences between lumiracoxib and the NSAID comparators were not statistically significantly different in either sub-study. Depending on which analysis of the TARGET study one considers, the conclusions may be very different. The pre-specified primary analysis would suggest that lumiracoxib, a highly COX-2 selective agent, is indistinguishable from two non-selective agents with

regard to the risk of serious adverse CV effects. The sub-study results, however, would suggest that lumiracoxib may be associated with a slightly increased CV risk compared to naproxen and a slightly decreased CV risk compared to ibuprofen. The cross sub-study comparison of naproxen and ibuprofen, however, would suggest no difference in CV risk for these non-selective NSAIDs. Overall, this study does not support a clear distinction between lumiracoxib and the non-selective NSAIDs.

The Etoricoxib versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness Trial (EDGE) compared etoricoxib 90 mg once daily versus diclofenac for up to 16 months in approximately 7100 patients with osteoarthritis. The relative risk for serious adverse CV events was 1.07 for the comparison of etoricoxib to diclofenac (not significantly different). EDGE, therefore, is another large controlled clinical trial that did not distinguish COX-2 selective and non-selective NSAIDs with regard to CV risk.

Non-selective NSAIDs

Long-term placebo- and active-controlled trials are generally not available for the non-selective NSAIDs, with the exception of the studies noted above where certain non-selective NSAIDs were used as active controls in studies of COX-2 selective drugs.

Observational studies

Data are available from a number of published and unpublished observational studies to address the issue of increased risk of serious adverse CV events for COX-2 selective and non-selective NSAIDs. These studies have utilized a variety of designs, methods, source databases, and comparison groups, and each study has been characterized by strengths and weaknesses. In most of the observational studies, the estimated relative risks of the COX-2 selective NSAIDs have ranged from 0.8 to 1.5, with many point estimates not achieving statistical significance. These data were presented and discussed in detail at the AC meeting and the committee members generally agreed that the observational data could not definitively address the question of a modestly increased CV risk for the COX-2 selective compared to the non-selective NSAIDs, with the possible exception of data on rofecoxib 50 mg.

Overall, the most consistent finding for increased CV risk was observed for rofecoxib 50 mg, where statistically significant relative risks of approximately 2 and 3 were seen in two studies. The signal for increased CV risk for the 25 mg rofecoxib dose, however, was smaller and did not consistently achieve statistical significance. The relative risks in the seven observational studies for celecoxib ranged from 0.4 to 1.2, with statistical significance observed once for a lowered risk and once for a higher relative risk. The available data for the non-selective NSAIDs from the observational studies are limited, and no consistent signals were observed.

Analysis and Conclusions

As noted above, the most persuasive evidence in support of an increased risk of serious adverse CV effects of the COX-2 selective NSAIDs is derived from a small number of long-term placebo- and active-controlled clinical trials in patients with arthritis or in the disease prevention setting. The data from these trials, however, are not consistent in demonstrating an increased risk of serious adverse CV effects for COX-2 selective drugs. Perfect replication of study results cannot be expected, and is not required to reach a valid scientific conclusion. However, the degree of inconsistency observed in the data from long-term controlled clinical trials has a considerable impact on

our ability to reach valid conclusions about the absolute magnitude of increased risk and to make risk versus benefit determinations for particular doses of specific drugs.

The data from controlled clinical trial comparisons of COX-2 selective and non-selective NSAIDs do not clearly demonstrate an increased relative risk for the COX-2 selective drugs, despite the substantial size of these studies. Only VIGOR clearly indicates such a difference with CLASS and EDGE giving no suggestion of a difference and TARGET giving analysis-dependent results. These findings, and the absence of any long-term placebo- or active-controlled clinical trials for most of the non-selective NSAIDs, make it difficult to conclude that the COX-2 selective drugs as a class have greater CV risks than non-selective NSAIDs. The data from the well-controlled observational trials also have not provided consistent assessments of risk when comparing COX-2 selective and non-selective NSAIDs. The point estimates of the relative risk comparisons from these data are mostly in a range where interpretation may be difficult and influenced by uncontrolled residual confounding or biases often inherent in the design and data limitations of these studies

Despite the limitations of the available data, overall, there is evidence, principally from a small number of placebo-controlled trials, that the approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib, valdecoxib) are associated with an increased risk of serious adverse CV events (e.g., MI, stroke, and death). It remains unclear, however, that it is the presence of, or the degree of, COX-2 selectivity that accounts for these observations, as some have hypothesized. As noted above, in various controlled clinical trials, COX-2 selective drugs have been indistinguishable from non-selective NSAIDs (i.e., ibuprofen, diclofenac) in studies of substantial size and duration. Further, although on theoretical grounds the addition of low-dose aspirin (a COX-1 inhibitor) to a COX-2 selective drug should resolve any increased CV risk caused by COX-2 selectivity, this effect has not in fact been observed in several studies in which such comparisons are possible. Taken together, these observations raise serious questions about the so called “COX-2 hypothesis,” which suggests that COX-2 selectivity contributes to increased CV risk. It, therefore, remains unclear to what extent the COX-2 selectivity of an individual drug predicts the drug’s potential for an increased risk of adverse CV events compared to drugs that are less COX-2 selective.

After carefully reviewing all the available data, we believe that the data are sufficient to support a conclusion that celecoxib, rofecoxib, and valdecoxib are associated with an increased risk of serious adverse CV events when compared to placebo. For celecoxib and rofecoxib these conclusions are primarily supported by the data from the APC and APPROVe trials, respectively. However, for celecoxib a nearly identical long-term placebo-controlled trial (the PreSAP trial) and a similarly sized placebo-controlled trial in patients at increased risk for Alzheimer’s disease did not replicate these findings. For rofecoxib, other long-term placebo-controlled trials of equal or greater duration (the Alzheimer’s treatment trials) did not replicate the APPROVe findings. There are no long-term placebo-controlled trial data for valdecoxib. It is difficult to know how to extrapolate the findings from the parecoxib/valdecoxib CABG trials to the chronic use situation given the significant physiologic and traumatic impact on the coronary vasculature during and following CABG surgery, and the systemic pro-inflammatory response resulting from heart-lung bypass. We believe, however, that it is reasonable from a public health perspective to assume that valdecoxib does not differ from the other

COX-2 selective agents with regard to increased CV risk with chronic use pending the availability of data from long-term controlled clinical trials that would indicate otherwise.

The long-term controlled clinical trial data comparing COX-2 selective agents (i.e., celecoxib, rofecoxib, lumiracoxib, etoricoxib) to non-selective NSAIDs are limited in number, but include several trials of very substantial size. They raise significant unresolved questions. First, rofecoxib 50 mg clearly appears to have an increased risk of serious adverse CV events compared to naproxen based on the data from the VIGOR trial.⁵ The absence of a placebo arm in the VIGOR trial, however, precludes a determination of whether chronic use of naproxen might also confer an increased risk of serious adverse CV events, albeit at a lower rate than rofecoxib. The VIGOR trial also does not provide a comparison between lower doses of rofecoxib and naproxen. Other controlled clinical trial data have also suggested some increased risk of serious adverse CV events for COX-2 selective agents versus naproxen (i.e., lumiracoxib in the naproxen sub-study in TARGET and etoricoxib in the NDA database); however, these studies also leave unresolved the question of whether naproxen is itself associated with an increased CV risk. The ADAPT trial is the only long-term controlled clinical trial in which a COX-2 selective agent and naproxen have been compared to placebo. The preliminary data from the ADAPT trial, however, do not appear to follow the pattern of the other COX-2 selective versus naproxen trials, showing a trend toward a higher event rate on naproxen compared to celecoxib and placebo (see above). Further, the cross sub-study comparison of naproxen and ibuprofen in TARGET suggests no difference in CV risk between these two non-selective NSAIDs. Taken together these data provide some support for the conclusion that a difference exists in the risk of serious adverse CV events between COX-2 selective agents and naproxen, but they do not provide any assurance that naproxen itself confers no increased CV risk; i.e., we cannot consider naproxen to be equal to or better than placebo.

The comparisons of COX-2 selective agents to certain other non-selective NSAIDs also raise interesting, and in the end unresolved, questions regarding the relative risk of COX-2 selective drugs compared to non-selective NSAIDs, despite the very large size of some of the trials. Several long-term controlled clinical trial comparisons of COX-2 selective agents to diclofenac have failed to provide evidence that diclofenac has a lower risk of serious adverse CV events than COX-2 selective agents (e.g., versus celecoxib in CLASS, versus etoricoxib in the NDA database, versus etoricoxib in EDGE). Large, long-term controlled clinical trial comparisons of COX-2 selective agents to ibuprofen, an unequivocally non-selective agent, also have failed to suggest a clear separation with regard to the risk of serious adverse CV events (e.g., versus celecoxib in CLASS, versus lumiracoxib in the ibuprofen sub-study in TARGET). While even these large studies cannot rule out a small true difference in CV risk between COX-2 selective agents and diclofenac and ibuprofen, they show no clear trend and are best interpreted as showing that the risk of serious adverse CV events between COX-2 selective agents and either diclofenac and ibuprofen are in fact very similar. The latter interpretation, taken together with the findings of an increased risk of serious adverse CV events from the long-term placebo-controlled clinical trials of COX-2 selective agents, would support

⁵ Rofecoxib 50 mg is not recommended for chronic use in the approved labeling for Vioxx. The higher dose of rofecoxib was used in the VIGOR trial to provide a “worst case” estimate of the risk of serious GI bleeding for rofecoxib in comparison to naproxen.

a conclusion that at least some of the non-selective NSAIDs are also associated with an increased risk of serious adverse CV events.

The inability to reliably estimate the absolute magnitude of the increased risk of serious adverse CV events for individual COX-2 agents, combined with the inability to reliably draw conclusions about the risk of COX-2 agents compared to one another or to other NSAIDs, highlights the conundrum the Agency faces in making decisions on appropriate regulatory actions. There is an urgent public health need to make appropriate regulatory decisions because the adverse events at issue are serious and a very large number of patients use selective and non-selective NSAIDs to treat chronic pain and inflammation. At the same time, erroneous conclusions and inappropriate actions are themselves potentially harmful to the public health. Although the currently available data are not definitive, the Agency cannot await more definitive data, which may take years to accumulate from studies that have not even begun, before taking action.

In summary, we conclude that the three approved COX-2 selective drugs are associated with an increased risk of serious adverse CV events, at least at some dose, with reasonably prolonged use. We do not believe, however, that the currently available data allow for a rank ordering of the approved COX-2 selective drugs with regard to CV risk. We also believe that it is not possible to conclude at this point that the COX-2 selective drugs confer an increased risk over non-selective NSAIDs in chronic use. Naproxen may be an exception, but the comparative data to COX-2 selective agents are not entirely consistent, we do not have adequate long-term placebo-controlled data to fully assess its potential CV risks, and the cross sub-study comparison to ibuprofen in TARGET does not suggest a lesser CV risk. For the vast majority of non-selective NSAIDs we do not have any data that allow comparisons with COX-2 selective agents for CV risk, and where data exist, primarily from very large studies, they do not consistently demonstrate that the COX-2 agents confer a greater risk. Finally, there are no data from long-term placebo-controlled trials for the non-selective NSAIDs (other than the preliminary data for naproxen from ADAPT) that are analogous to the data available for the COX-2 selective agents.

The absence of long-term controlled clinical trial data for the non-selective NSAIDs significantly limits our ability to assess whether these drugs may also increase the risk of serious adverse CV events. The long marketing history of many of these drugs cannot be taken as evidence that they are not associated with an increased risk of serious adverse CV events since CV events occur fairly commonly in the general population and small increases in common adverse events are impossible to detect from spontaneous reporting systems. The adverse CV risk signal for the COX-2 selective drugs became apparent only from large, long-term controlled clinical trials and large retrospective cohort studies. Similar clinical trials are needed to assess the potential risks of the non-selective NSAIDs.

Given our inability to conclude, based on the available data, that the COX-2 selective agents confer an increased risk of serious adverse CV events compared to non-selective NSAIDs, we believe that it is reasonable to conclude that there is a “class effect” for increased CV risk for all NSAIDs pending the availability of data from long-term controlled clinical trials that more clearly delineate the true relationships. This interpretation of the available data will serve to promote public health by alerting physicians and patients to this class concern and will make it clear that simply switching from a COX-2 selective agent to a non-selective NSAID does not mean that the potential for increased risk of serious adverse CV events has been fully, or even partially, mitigated.

With a “class effect” of NSAIDs on CV risk as a baseline, other factors must be considered in determining the overall risk versus benefit profile for individual drugs within the class and what, if any, regulatory actions are appropriate. Some of the factors that must be considered include any demonstrated benefit of a given drug over other drugs in the class (e.g., superiority claims, effectiveness in patients who have failed on other drugs) and any unique toxicities (or absence of a toxicity) of a given drug over other drugs in the class.

With regard to greater or special effectiveness, while it is widely believed that patients differ in their response to NSAIDs, there are no controlled clinical trial data (e.g., studies in non-responders to a particular NSAID) to support such conclusions. Nonetheless, despite the lack of rigorous evidence, this widely accepted belief is at least in part a valid rationale for maintaining a range of options in the NSAID class from which physicians and patients may choose. In addition, as noted above, there is no basis for concluding that the risk of serious adverse CV events for some NSAIDs is worse than the risk for the others, which supports maintaining a range of options.

With regard to toxicities, the primary goal in developing COX-2 selective agents was to reduce the serious, and often life-threatening, risk of gastrointestinal (GI) bleeding associated with chronic use of all NSAIDs. To date, the only COX-2 selective agent that has demonstrated a reduced risk for serious GI bleeding is rofecoxib, but only in comparison to naproxen. All of the approved COX-2 selective agents have been shown to reduce the incidence of GI ulcers visualized at endoscopy compared to certain non-selective NSAIDs, but the clinical relevance of this finding as a predictor of serious GI bleeding has not been confirmed (e.g., no difference in serious GI bleeding was observed in CLASS). Improved GI tolerability of NSAIDs is an important issue from an individual patient and public health perspective and is, at least in part, a valid rationale for maintaining a range of options in the NSAID class from which physicians and patients

may choose. Besides the COX-2 selective NSAIDs, other strategies are available that may reduce the risk of GI bleeding with NSAIDs (e.g., combined use of a non-selective NSAID with misoprostol or a proton pump inhibitor), but data are currently lacking on how these strategies compare to the use of COX-2 selective drugs. With the exception of the comparison of rofecoxib to naproxen, data are not available to confirm a reduced risk of serious GI bleeding for the COX-2 selective agents, though it is widely believed that these agents are better tolerated by many patients.

In addition to the risk of serious and potentially life-threatening GI bleeding, NSAIDs are also associated with other potentially serious adverse effects, including, but not limited to, fluid retention, edema, renal toxicity, hepatic enzyme elevation, and bronchospasm in patients with aspirin-sensitive asthma. Comparative data to differentiate NSAIDs from one another with regard to these adverse effects are generally not available or are inconclusive.

Boxed warnings are currently included in the approved labeling for two single ingredient NSAID products.⁶ Bextra (valdecoxib) has a boxed warning for serious and potentially life-threatening skin reactions (i.e., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme). Toradol (ketorolac) has a boxed warning emphasizing that it is approved only for short-term (≤ 5 days) use in patients with moderately severe acute pain that requires analgesia at the opioid level, usually in a post-operative setting. Toradol is the only NSAID indicated for treatment of pain available for parenteral use (i.e., IV or IM injection); it therefore provides an important therapeutic option for physicians and patients in settings where the patient cannot take analgesics by mouth.⁷ This therapeutic advantage favors continued availability of Toradol, despite the need for a boxed warning about the potential for increased frequency of serious adverse reactions with long-term (≥ 5 days) use. In contrast, there are no data to support a unique therapeutic benefit for Bextra over other available NSAIDs, which might offset the increased risk of serious and potentially life-threatening skin reactions. While other COX-2 selective and non-selective NSAIDs also have a risk for these rare, serious skin reactions, the reported rate for these serious side effects appears to be greater for Bextra than for other COX-2 agents.⁸ To date, the agency has received 7 reports of deaths from serious skin reactions in patients following treatment with Bextra. The occurrence of these serious skin reactions in individual patients is unpredictable, occurring with and without a history of sulfa allergy (valdecoxib is a sulfonamide) and after both short- and long-term use, which makes attempts to manage this increased risk difficult.

⁶ The package insert for Arthrotec, a combination of diclofenac and misoprostol, includes a boxed warning, but the warning relates to potential toxicities of misoprostol, not diclofenac.

⁷ Indomethacin is also available as a parenteral formulation, but is only indicated for parenteral use for treatment of patent ductus arteriosus.

⁸ The agency has recently received a Citizens Petition regarding the risk of Stevens-Johnson syndrome with ibuprofen (February 15, 2005). Although the petition is currently under review, and the agency has not reached a decision on the requested actions, based on analyses of data obtained before the petition was submitted, the agency has determined that the labeling for non-prescription NSAIDs should be updated to warn of the potential for skin reactions. Accordingly, along with the changes to the label to address CV risks, the agency will ask manufacturers of non-prescription NSAIDs to make these changes. After we have completed our review of the petition, we may determine that additional labeling changes with regard to potential skin reactions are warranted. The risk for serious skin reactions is already included in the labeling for most prescription NSAIDs.

Several non-selective NSAIDs are currently available to consumers without a prescription (e.g., ibuprofen, naproxen, ketoprofen). The non-prescription doses of these products are generally well below the maximum daily prescription doses for the same active ingredient and the duration of treatment without specific alternate instructions from a physician is limited to 10 to 14 days. The applicability of the increased risk of serious adverse CV events as described above from controlled clinical trials to low-dose, short-term use of these non-prescription products for the relief of acute pain is unclear, although any such risk is expected to be minimal. No signal for increased risk of serious adverse CV events has been detected in the short-term controlled clinical trials that supported the approval of these agents for treatment of acute pain. While these studies were primarily designed to evaluate effectiveness, the absence of a signal of increased CV risk provides some reassurance of the safety of short-term use. Further, with the exception of the parecoxib/valdecoxib CABG studies, the increased risk of serious adverse CV events in the controlled clinical trials described above have only become apparent after months to years of treatment. The parecoxib/valdecoxib data also provide support for the safety of short-term use. The two short-term placebo-controlled CABG studies showed an increased risk of serious CV events, but, a short-term placebo-controlled trial in general surgery patients did not show an increased risk. These data may suggest that in the absence of a predisposing condition, such as recent CABG surgery, the CV risk of short-term use of NSAIDs is very small, if any, particularly at low doses and given the typically intermittent nature of use of non-prescription NSAIDs for relief of acute pain.

Aspirin is also an NSAID that is available and widely used without a prescription. However, aspirin has other unique pharmacologic properties, including irreversible inhibition of platelet function, that distinguish it from the rest of the NSAID class. Further, data from long-term controlled clinical trials have clearly demonstrated that aspirin significantly reduces the risk of serious adverse CV events in certain patient populations (e.g., patients with a history of a MI). Aspirin, therefore, is an exception to the apparent “class effect” of increased risk for serious adverse CV events for NSAIDs described above. Data from large, long-term controlled clinical trials clearly showing no increased CV risk or a reduction in CV risk would be necessary before concluding that other NSAIDs are also exceptions to the class risk.

Recommendations

We summarize below our recommendations for appropriate regulatory actions for the NSAID class and select individual agents.

NSAIDs as a class

Boxed Warning and Contraindication

We recommend that the professional labeling (package insert) for all prescription NSAIDs, including both COX-2 selective and non-selective drugs, be revised to include a boxed warning highlighting the potential increased risk of CV events. The boxed warning should also include the well described risks of serious, and often life-threatening GI bleeding. We believe that a boxed warning with regard to potential increased CV risk is an appropriate response to the currently available data and will serve to highlight to physicians and patients that they must carefully consider the risks and benefits of all NSAIDs, as well as other available options, before deciding on a treatment plan for relief of chronic pain and inflammation. If it is determined that chronic use of an NSAID is

warranted for an individual patient, the boxed warning will help to emphasize the importance of using the lowest effective dose for the shortest duration possible along with appropriate attention to reduction of other risk factors for cardiovascular disease. The language of the boxed warning should be standardized across the class, with the exception of those situations where specific data or other information is available for an individual drug. In those cases, the standardized class wording should be maintained and the drug specific information added, including the results of any large controlled clinical trials.

The recommendation for a boxed warning for potential increased risk of CV events is supported by the unanimous vote of the Advisory Committees (28 yes) on the question of whether the labeling for the non-selective NSAIDs should be modified to include the absence of long-term controlled clinical trial data to assess the potential CV effects of these drugs.⁹ While the AC did not specifically vote on a boxed warning, many of the committee members commented that such a warning would be an appropriate response given the current data. The Advisory Committees also strongly supported boxed warnings for the individual COX-2 selective drugs for increased CV risk.

The recommendation that the boxed warning also include the well recognized serious, and often life-threatening, risk of GI bleeding associated with chronic use of NSAIDs is intended to further reinforce the existing bolded warning. The GI bleeding risk with NSAIDs is clearly consistent with our current approach to the use of boxed warnings, and placing this information in a boxed warning will serve to further emphasize this serious risk and ensure that physicians and patients keep this risk in mind as they are considering options for chronic therapy of pain and inflammation.

We also recommend that the labeling for all NSAIDs include a contraindication for use in patients in the immediate post-operative setting following CABG surgery. Data are only available in this setting from valdecoxib, but we have concluded that this short-term increased CV risk should be extrapolated to long-term use of valdecoxib. It is logical to also extrapolate this finding to other NSAIDs, pending the availability of other data that would suggest otherwise given the serious nature of the adverse events noted in the valdecoxib CABG study and the high-risk nature of the patients undergoing CABG surgery. The contraindication for NSAID use in this setting would NOT apply, however, to aspirin for the reasons noted above.

⁹ There were 32 voting members of the Advisory Committees, but 4 members had left the meeting by the time this question was discussed.

Medication Guide

We recommend that the patient labeling for all prescription NSAIDs, including both COX-2 selective and non-selective drugs, include a Medication Guide. The Medication Guide should focus on the potential increased risk of serious adverse CV events and the risks of serious GI bleeding. The Medication Guide will also inform patients of the need to discuss with their doctor the risks and benefits of using NSAIDs and the importance of using the lowest effective dose for the shortest duration possible if treatment with an NSAID is warranted. To avoid confusion and to allow for more rapid implementation, we recommend that the text of the Medication Guide be standardized across the class, following the model that was recently successfully implemented for antidepressants.

Comprehensive Data Review and New Studies

We recommend that the agency request that the sponsors of all non-selective NSAIDs conduct and submit for FDA review a comprehensive review and analysis of all available data from controlled clinical trials to further evaluate the potential risk of serious adverse CV events. The search and analysis strategy should be similar across sponsors and drugs. The agency should carefully review the data as they become available and take any appropriate regulatory actions based on the findings.

The agency should also work closely with sponsors of non-selective NSAIDs and other stakeholders (e.g., NIH, professional associations, patient groups) to encourage the conduct of additional long-term controlled clinical trials of the non-selective NSAIDs to better evaluate the potential for increased risk of serious adverse CV events.

Non-prescription NSAIDs

We recommend that the NSAIDs that are currently available without a prescription for the short-term treatment of acute pain continue to be available to consumers. While this would apparently represent the first time that products that have a boxed warning in the prescription package insert would also be available for non-prescription use, we believe the available data support a conclusion that short-term use of low doses of the available non-prescription NSAIDs is not associated with an increased risk of serious adverse CV events. The overall benefit versus risk profile for the non-prescription NSAIDs remains very favorable when they are used according to the labeled instructions, and we believe that it is important to maintain a range of therapeutic options for the short-term relief of pain in the OTC market. Further, the other available non-prescription drugs for short-term relief of pain and fever can also be associated with serious, and potentially life-threatening, adverse events in certain settings and patient populations.

To further encourage the safe use of the non-prescription NSAIDs, we believe that the labeling for these products should be revised to include more specific information about the potential CV and GI risks, instructions about which patients should seek the advice of a physician before using these drugs, and stronger reminders about limiting the dose and duration of treatment in accordance with the package instructions unless otherwise advised by a physician. In addition, as noted earlier, the agency has determined that the labeling for non-prescription NSAIDs should be revised to warn of the potential for skin reactions. We also recommend that the Agency continue its current consumer

education efforts regarding the safe and effective use of non-prescription pain relievers and that this new information be highlighted in those campaigns.

CELEBREX®, NDA 20-998/NDA 21-156 (celecoxib capsules)

After carefully reviewing all the available data, we conclude that the benefits of celecoxib outweigh the potential risks in properly selected and informed patients. Therefore, we recommend that celecoxib remain available as a prescription drug with the revised labeling described below in addition to the NSAID class boxed warning, contraindication, and Medication Guide described above.

Boxed warning and other labeling changes

We recommend that the boxed warning for Celebrex include specific reference to the controlled clinical trial data that demonstrate an increased risk of serious adverse CV events (e.g., the APC trial). The text in the box may be brief and include a reference to the CLINICAL PHARMACOLOGY, Clinical Studies section of the labeling where the available long-term controlled clinical trial data should be described in greater detail. Finally, we recommend that the INDICATIONS section of the labeling be revised to clearly encourage physicians to carefully weigh the potential benefits and risks of celecoxib and other treatment options for the condition to be treated before a decision is made to use Celebrex, and to use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

Postmarketing study commitment

We strongly recommend that CDER request a written commitment from the sponsor to conduct an additional long-term study (or studies) to address the safety of celecoxib compared to naproxen and other appropriate active controls (e.g., other non-selective NSAIDs, appropriate non-NSAID active comparators). CDER should be actively involved in the design of the trial(s) and insist on aggressive timelines for initiation and completion of the study(ies).

The above recommendations are consistent with the votes and recommendations made by the Advisory Committees for Celebrex. The Advisory Committees were unanimous in their conclusion that an increased risk of cardiovascular adverse events has been demonstrated for celecoxib. After carefully considering all the available data, the Advisory Committees voted 31 yes to 1 no in response to the question: “Does the overall risk versus benefit profile of celecoxib support marketing in the US?” While specific votes were not taken on the issue of what labeling changes and other risk management options would be appropriate, the overwhelming majority of the Advisory Committee member voiced their support for a boxed warning, a Medication Guide, and postmarketing study commitments to further explore the long-term safety of Celebrex in comparison to other appropriate comparators.

BEXTRA®, NDA 21-341 (valdecoxib tablets)

After carefully considering all the available data and risk management options, we have concluded that the overall risk versus benefit profile for Bextra is unfavorable at this time. We therefore recommend that Bextra be withdrawn from the U.S. market. We have concluded, as noted above, that Bextra has been demonstrated to be associated with an increased risk of serious adverse CV events in short-term CABG trials and that it is reasonable from a public health perspective to extrapolate these findings to chronic use. The increased risk of serious adverse CV events alone, however, would not be sufficient to warrant withdrawal of Bextra since we have no data showing that Bextra is worse than

other NSAIDs with regard to CV risk. Our recommendation for withdrawal is based on the fact that, in addition to this CV risk, valdecoxib already carries a boxed warning in the package insert for serious, and potentially life-threatening, skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme) and FDA has received 7 spontaneous reports of deaths from these reactions. The reporting rate for these serious skin reactions appears to be greater for Bextra than other COX-2 selective agents. Further, the risk of these serious skin reactions in individual patients is unpredictable, occurring in patients with and without a prior history of sulfa allergy, and after both short- and long-term use, which makes risk management efforts difficult. To date, there have been no studies that demonstrate an advantage of valdecoxib over other NSAIDs that might offset the concern about these serious skin risks, such as studies that show a GI safety benefit, better efficacy compared to other products, or efficacy in a setting of patients who are refractory to treatment with other products.

The recommendation that Bextra be withdrawn is supported, at least in part, by the specific votes and recommendations of the Advisory Committees. The Advisory Committees were unanimous in their conclusion that an increased risk of cardiovascular adverse events has been demonstrated for valdecoxib. In response to the question “Does the overall risk versus benefit profile of valdecoxib support marketing in the US?” the Advisory Committees voted 17 yes and 13 no with 2 abstentions. Several of the advisory committee members who voted no expressed concerns about the strong signal of CV risk from the CABG trials, the absence of long-term controlled trial data to more clearly define the potential CV risks of Bextra, the fact that Bextra already carried a boxed warning for serious skin reactions, and the fact that there were no data to support a conclusion that Bextra offered a therapeutic advantage over NSAIDs.

One potential argument in favor of continued marketing of valdecoxib is that it provides an additional therapeutic option for management of arthritis and that prescribers and patients could be informed of the potential increased risk of CV events and serious GI bleeding, in addition to the potential for serious and possibly life-threatening skin reactions, and be allowed to make individualized treatment decisions. This approach, in fact, was strongly favored by practicing rheumatologists on the Advisory Committee. It is important to note, however, that there are more than 20 other NSAIDs on the market. This range of options diminishes the value of continued marketing of valdecoxib, particularly in the face of an already existing boxed warning regarding serious, and potentially life-threatening, skin reactions and the fact that there are no data that demonstrate that valdecoxib offers any therapeutic advantage over other NSAIDs.

We recommend that FDA request that Pfizer voluntarily withdraw Bextra from the U.S. market. If Pfizer does not agree to that request, we recommend that FDA initiate the formal withdrawal process by preparing and publishing a Notice of Opportunity for Hearing.

We recommend that FDA remain open to allowing limited access to valdecoxib under an IND to those patients who believe that it is their best option, if the sponsor proposes such an IND. If additional clinical trials subsequently demonstrate that valdecoxib does not have an increased CV risk (or if its risk is significantly less than other available agents) or a therapeutic advantage for valdecoxib over other NSAIDs, FDA should carefully consider those data and reassess the current conclusions regarding the overall risks and benefits for valdecoxib.

VIOXX ®, NDA 21-042 (rofecoxib tablets and oral suspension)

VIOXX was voluntarily withdrawn from the U.S. market by the sponsor on September 30, 2004, following the announcement of the results from the APPROVe trial. Therefore, no regulatory action is warranted at this time. Should the sponsor seek to resume marketing for rofecoxib, a supplemental NDA with revised labeling will be required. The supplemental NDA would require FDA review and approval prior to implementation of the new labeling since the changes would not be of the type allowed under FDA regulations for a “Changes Being Effectuated (CBE)” labeling supplement. The supplemental application should specifically outline the sponsor’s proposal for revised labeling designed to provide for safe and effective use of the drug in populations where the potential benefits of the drug may outweigh potential risks, and all data and arguments that support resumption of marketing.

We believe that FDA should carefully review any such proposal submitted by the sponsor. We would also recommend that the FDA Drug Safety Oversight Board (DSB) and an advisory committee be consulted before a final decision is taken. Our rationale for recommending review by the DSB and an advisory committee includes the following factors. First, there is limited precedent for a drug that has been withdrawn from the U.S. market for safety reasons to be returned to marketing. The only recent example that we can recall was Lotronex, and that application was reviewed by an advisory committee before FDA reached a final decision on the sponsor’s request.¹⁰ Second, concerns were expressed at the recent advisory committee meeting that Vioxx may be associated with a higher risk of increased blood pressure, fluid retention, and congestive heart failure than other COX-2 selective NSAIDs. We believe that these additional potential serious risks of Vioxx need to be fully explored through a public process before a decision is made regarding resumed marketing. Third, the recent advisory committee meeting was a general issues meeting, not one specifically devoted to the issue of resumption of marketing of Vioxx. While the committees narrowly voted in the affirmative that the overall risk versus benefit profile of rofecoxib supported marketing in the U.S., the committee members expressed a wide variety of often contradictory opinions on what regulatory actions (e.g., labeling changes, risk management efforts) would be appropriate to allow resumed marketing. Specific votes were not taken on these important issues, and we believe the agency would benefit from the advice of an advisory committee meeting specifically devoted to the resumption of marketing of Vioxx before the FDA reaches a decision on final action. Finally, the withdrawal of Vioxx has been the subject of intense public interest and debate, and we believe that a transparent process for reaching an agency decision on resumption of marketing is needed to ensure public confidence in the agency’s decision-making process.

¹⁰ The FDA Drug Safety Oversight Board had not been established at the time of the review of the Lotronex resubmission.

APPENDIX C. NUMBER OF PRESCRIPTIONS BY AGE AND DOSING

Dosing by Medication and Age Bin								
	[41.28,46.78)		[46.78,52.27)		[52.27,57.77)		[57.77,63.26)	
Med	Low	High	Low	High	Low	High	Low	High
% COX-2	29.3		38.3		50.4		59.2	
Valdecoxib	31493	4671	46558	5735	62399	6441	81151	6876
Celecoxib	61926	28341	100618	48903	136127	71143	172699	90822
Meloxicam	30196	1328	39285	1672	46028	1887	54803	1963
Ibuprofen	101648	241217	105151	243261	78397	184072	65971	140582
Naproxen	147306	14467	157100	16297	132597	15569	118144	14574
Rofecoxib	74941	21080	117080	30429	155651	34799	187625	36540
	[63.26,68.75)		[68.75,74.25)		[74.25,79.74)		[79.74,85.23)	
Med	Low	High	Low	High	Low	High	Low	High
%COX-2	66.6		71.9		74.6		78.8	
Valdecoxib	116166	8246	142930	7776	104321	5079	76104	2784
Celecoxib	253139	120300	303508	130174	241625	92606	196770	63748
Meloxicam	65041	2199	66646	2046	48400	1426	33379	832
Ibuprofen	67622	125013	66139	97216	47595	54648	31530	27701
Naproxen	124178	15758	111631	14252	73912	8951	42074	4903
Rofecoxib	256400	41808	293641	38301	221913	25191	165578	15706
	[85.23,90.73)		[90.73,107.21]					
Med	Low	High	Low	High				
%COX-2	81.1		84.5					
Valdecoxib	26324	712	5113	131				
Celecoxib	75720	21468	17817	4067				
Meloxicam	10913	235	1735	27				
Ibuprofen	10866	8047	2366	1210				
Naproxen	13012	1337	2012	267				
Rofecoxib	60736	5057	13471	858				

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APPENDIX D. ESTIMATED COEFFICIENTS FOR THE LOGISTIC REGRESSION MODEL

Coefficients:

	Value	Std Error	Z value
(Intercept)	-8.716	0.130	-67.106
Celecoxib	-0.066	0.032	-2.063
Meloxicam	-0.072	0.049	-1.474
Ibuprofen	-0.238	0.041	-5.853
Naproxen	-0.171	0.041	-4.140
Rofecoxib	0.09	0.032	2.802
High Dose	0.039	0.024	1.618
Age 02	0.475	0.103	4.584
Age 03	0.888	0.100	8.878
Age 04	1.333	0.098	13.670
Age 05	1.670	0.096	17.476
Age 06	1.999	0.095	21.125
Age 07	2.298	0.095	24.242
Age 08	2.622	0.095	27.592
Age 09	2.753	0.098	28.042
Age 10	3.033	0.111	27.283
BENCATDA	-0.125	0.174	-0.716
BENCATDGR	0.060	0.275	0.217
BENCATDR	0.272	0.122	2.223
BENCATDS	0.441	0.124	3.562
BENCATGRD	0.122	0.188	0.650
BENCATIGR	-4.803	223.216	-0.022
BENCATOTH	0.045	0.514	0.088
BENCATRET	0.715	0.122	5.850
BENCATZ	0.188	0.178	1.052

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