

MEMORANDUM

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FROM: John K. Jenkins, M.D.
Director, Office of New Drugs (OND)

and

Paul J. Seligman, M.D., M.P.H
Director, Office of Pharmacoepidemiology 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.

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.

- 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.
- 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:

- 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 Pharmacoepidemiology 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

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.

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.

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.

Valdecoxib

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.

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.

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.

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 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

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.

sulfonamide) and after both short- and long-term use, which makes attempts to manage this increased risk difficult.

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 anti-depressants.

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 Effected (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

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

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.