FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

M E M O R A N D U M

DATE: October 31, 2006

FROM: Bob A. Rappaport, MD
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Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Arthritis Advisory Committee (AAC)

RE: Overview of the November 29, 2006 AAC Meeting to Discuss NDA 20-998, Supplement 021, for Celebrex for the treatment of Juvenile Rheumatoid Arthritis

One of the results of the withdrawal of Vioxx from the market in September of 2004 due to safety concerns is that an increased level of scrutiny has been be applied to Cox-2 Inhibitor, and perhaps to all NSAID drug products, by the Agency, the pharmaceutical industry, academia, the press, various advocacy groups and Congress. As part of this process, numerous analyses of the available data regarding the potential cardiovascular toxicity of Celebrex have been performed, and numerous articles have been published on this subject. To date, while there is a fairly clear signal of increased risk for cardiothrombotic adverse events in adults, the exact degree of this risk and the underlying pathophysiology for these events remain controversial.

Pfizer, Inc. submitted a supplement to their NDA for Celebrex on June 20, 2006, in support of a new indication, and the addition of new safety data, pharmacokinetic data, and dosing and administration recommendations to the product label, for the treatment of Juvenile Rheumatoid Arthritis (JRA). JRA is an often devastating disease that affects approximately 30,000 to 60,000 children in the United States, and that is associated with joint swelling, pain, decreased range of motion and abnormalities of growth and development. In some cases, systemic complications may occur including uveitis, a chronic inflammation of the eye. In severe, uncontrolled cases permanent disability may occur due to progressive joint damage. While there are other drug products approved for

the treatment of this disorder, for some patients these approved products may provide limited efficacy or intolerable side effects. Thus, it is important that we support the development of new pharmaceutical products, as well as non-pharmaceutical therapies, to intervene when the available treatments have not been successful.

This meeting of the AAC is critical to the Agency's assessment of and final decision on the approvability of Pfizer's application. As experts in the areas of rheumatology, pediatric rheumatology, pain, clinical trial design, risk management and ethics, your input is essential to our understanding of the final balance of the benefit and the risk of the use of Celebrex for JRA, and whether or not that balance is one that merits the approval for marketing of this product for this patient population.

During this meeting, representatives from the Agency and Pfizer will present:

- a summary of our current understanding of the cardiovascular risks associated with Celebrex and the other Cox-2 inhibitors, as well as the non-selective NSAIDS;

- the current paradigms used in the treatment of JRA, and the effectiveness and adverse event profiles of these treatments; and

- the results of Pfizer's pre-clinical and clinical studies performed in support of their application.

We will attempt to provide a thorough and complete foundation for later discussion, and to answer any questions you have regarding the data resulting from the studies, the analyses performed by the sponsor and the Agency review staff, and any related regulatory issues. These presentations and responses, along with the valuable input that you will hear from interested parties during the Open Public Hearing portion of the meeting, will, hopefully, allow for an in-depth and informed discussion of the questions that will be posed to you.

In the afternoon session, you will be asked to address the apparent risks and benefits associated with the use of Celebrex in the treatment of JRA. In particular, as the long-term cardiovascular risks to a child treated with Celebrex may not be clear based on the currently available data and our limited understanding of the underlying pathophysiology, you will be asked to assess the value of employing this treatment in the face of an unclear level of risk. We will also be asking you to consider the need for further studies of the effectiveness and toxicity associated with Celebrex use in JRA and, if studies are warranted, to help us define an appropriate path forward for those investigations.

The Division and the Agency are grateful to the members of the committee and our invited guests for taking time from your busy schedules to participate in this important meeting. The approval of new pharmaceutical products for children inevitably raises particular concerns for the Agency review staff; and the approval of a product with a less than well-defined toxicity profile makes our assessment even more complex, and requires

a high level of caution. Thank you in advance for helping us to make the most informed and appropriate decision possible.

Celebrex for JRA: Risk-Benefit Analysis

Jeffrey Siegel, M.D., Team Leader, FDA/CDER/OND/ODE2/DAARP

In considering whether to approve celecoxib (Celebrex) for children with juvenile rheumatoid arthritis (JRA), it is important to carefully weigh the evidence supporting its effectiveness as well as concerns about its safe use in this patient population. JRA is a serious chronic arthritic condition of children that is associated with significant disability in many cases. Current drug treatment of JRA consists of non-steroidal anti-inflammatory drugs (NSAID's) for their anti-inflammatory and analgesic effects and disease modifying agents, such as methotrexate (MTX), leflunomide and TNF-blocking agents. While several NSAID's are currently approved for children it is common for physicians to have to try a variety of different ones before finding one that provides adequate pain relief without unacceptable side effects in an individual patient. Therefore providing additional options for pain relief for children with JRA is an important goal.

Assessing the efficacy of celecoxib in JRA

To assess the efficacy of the COX-2 selective NSAID celecoxib in JRA Pfizer used a non-inferiority design comparing the benefits of celecoxib with naproxen. The study was a 3-month, randomized, double-blind, active controlled study comparing celecoxib 12 mg/kg/d and celecoxib 6 mg/kg/d with naproxen 15 mg/kg/d. The primary endpoint was the percent of patients achieving a JRA DOI (definition of improvement) 30. The study was designed to rule out a margin of non-inferiority of celecoxib to naproxen exceeding 25% based on the 95% confidence interval. The trial was successful in establishing non-inferiority of both doses of celecoxib to naproxen based on the prespecified 25% margin. Furthermore, improvements were seen in all the components of the JRA DOI30: physician and parent global assessment, functional ability, joints with limited range of motion and C-reactive protein.

How definitive are these results in establishing the efficacy of celecoxib in children with JRA? To fully understand the significance of the efficacy results it is important to appreciate how non-inferiority trials are designed and what some of their pitfalls are. In a randomized, placebo-controlled trial efficacy is established based on the improved outcome in patients receiving the study drug compared with those receiving placebo. In contrast, in a non-inferiority design efficacy is established based on seeing no difference (or only a small difference) between study drug and the known effective active comparator. In diseases where improvement is rare without treatment this type of design is generally not problematic because any improvement can be ascribed to study drug. However in many diseases, like JRA, it is common to see improvement even in patients in the placebo control arm of clinical trials. Indeed, in a recent placebo-controlled trial of infliximab in JRA it was reported that approximately 50% (47%) of children receiving placebo experienced an improvement over 3 months using the JRA DOI30 (DJ Lovell et al. abstract #1954. *Arthritis & Rheumatism. 52(9):S724, 2005*). Therefore, a high response rate with study drug in a non-inferiority study does not always indicate efficacy. It is also important to consider what the placebo response would have been if a placebo arm had been included.

Another challenge in evaluating data from non-inferiority studies is that for certain drug classes there are instances where known efficacious products may fail to show superiority to placebo in individual randomized trials. Examples of such drug trials include trials of anti-depressants and trials of beta-blockers for secondary prevention of acute MI. A product like this that sometimes fails to show efficacy in clinical trials would be a poor choice as the active comparator in a non-inferiority study of a new drug because a similar outcome for the two study arms could indicate that both drugs are effective or that they are both ineffective. For this reason it is important to have evidence that a drug used as an active comparator has consistent evidence of efficacy in randomized trials.

Non-inferiority studies establish efficacy of study drug statistically by demonstrating that any inferiority to the active comparator is no greater than some small amount, the allowable non-inferiority margin. If there is an expected placebo response then the non-inferiority margin must be set small enough that responses to study drug that are similar to placebo responses would not lead to the erroneous conclusion of efficacy when study drug was in fact no different from placebo. Non-inferiority margins are ordinarily set in one of two ways. For active comparator drugs with response rates that are consistently higher than placebo a non-inferiority margin can be set as some fraction of the effect size (i.e., response rate with drug minus response rate with placebo). For example if the non-inferiority margin is set at one-quarter the effect size then the study drug can be shown to be no more than one-quarter less effective than the active comparator. In some instances data are not available from placebo-controlled trials of active comparators but these drugs are nonetheless considered to be highly efficacious (for example, certain drugs for preventing renal transplant rejection or antimicrobials for certain infections). In these cases it may be unethical to conduct placebo-controlled studies and the non-inferiority margin may be set at a very small level that is considered a margin so small that it is clinically ignorable.

Unfortunately, in JRA insufficient information about the active comparator, naproxen, makes it problematic to design the non-inferiority study of celecoxib using one of the methods described above. There are no randomized, placebo-controlled studies of naproxen in JRA using the JRA DOI30 to establish an effect size. Therefore the first method cannot be used. To use the second method, i.e., choosing a non-inferiority margin that is clinically ignorable, it is necessary to determine what margin is appropriate and whether the non-inferiority margin of 25% specified for the celecoxib trial was appropriate. To evaluate the suitability of a non-inferiority margin for the celecoxib JRA trial it is necessary to make an assumption of what the placebo response would have been if a placebo arm had been included in the study. If the placebo response had been 47% as was observed in the infliximab trial, given that the response rate for the naproxen active comparator was 67%, the effect size for naproxen would be 20%. In this case a non-inferiority margin of 25% would be inadequate as it would not distinguish an efficacious product from placebo. A more appropriate margin would be one that preserved some proportion of the effect size of naproxen, e.g. half of that effect, or 10%.

For the reasons outlined above, the prespecified statistical plan for establishing efficacy of celecoxib using a 25% non-inferiority margin may not be adequate. Thus it is necessary to rely on exploring the totality of the data to determine whether the results of

the trial support efficacy of celecoxib in JRA. To reach a conclusion it is necessary to reach a judgment on 1) how well a placebo group would have done if one had been included 2) what is the effect size of the active comparator naproxen and 3) whether the non-inferiority margin of celecoxib vs. naproxen that was seen is adequate to conclude efficacy of celecoxib. If we assume the placebo response rate would have been 47% (as was reported for the recent infliximab trial) then the response rate for naproxen of 67% would indicate an effect size of 20%. Other estimates of the likely placebo response rate would provide different estimates of the effect size of the active comparator naproxen. The results of the celecoxib trial in JRA exclude a 13% margin of non-inferiority of celecoxib using the 95% confidence interval. At the advisory committee meeting, the Division will be asking the committee for their advice on whether these findings indicate efficacy of celecoxib.

In summary, the randomized trial of celecoxib demonstrated non-inferiority to naproxen based on the prespecified trial design using a non-inferiority margin of 25%. In support of the efficacy of celecoxib the point estimate for the response rate with celecoxib is identical to that seen with naproxen. Nonetheless, there are limitations to the design of this non-inferiority trial that raise questions about whether it provides adequate evidence of efficacy of celecoxib in JRA.

Assessing the safety of celecoxib in JRA

To assess the safety of celecoxib in JRA it is necessary to consider information from several different sources: the clinical trial data for celecoxib in JRA; the post-marketing data regarding off-label use of celecoxib in children; the risks and benefits of alternative products and the known adverse effects associated with the use of COX-2 selective and non-selective NSAIDs in adults. A key consideration in assessing the safety of celecoxib in JRA is the evidence of increased risk of cardiovascular adverse events in adults receiving prolonged treatment with non-selective and COX-2 selective NSAIDs, including celecoxib.

Data are available on the safety of treatment of JRA patients with celecoxib for up to 6 months at or above a dose approximating the dose proposed for marketing. In Study 195, 242 children were randomized to receive celecoxib 6 or 12 mg/kg/d or naproxen 15 mg/kg/d for 3 months. Following completion of the randomized, double-blind portion of the study 200 children enrolled in the open-label extension portion during which they received celecoxib 12 mg/kg/d for an additional 3 months. In the randomized portion of the trial for the celecoxib dose arm that approximates the dose proposed for marketing (6 mg/kg/d) the organ systems with the most common adverse events (AEs) were GI, infections and infestations and nervous system disorders. Compared to naproxen the only organ systems with more frequent AEs in the celecoxib 6 mg/kg/d arm were respiratory disorders, eye disorders and metabolic disorders. Overall, the common AEs seen with celecoxib 6 mg/kg/d were similar in type and frequency to those seen with naproxen.

Serious adverse events (SAEs) were observed more frequently in the celecoxib 6 mg/kg/d arm than with naproxen but there was no dose response as SAE rates were similar with celecoxib 12 mg/kg/d as with naproxen. The SAEs that were seen more frequently with

celecoxib included GI disorders, General Disorders and Administration Site Conditions and Musculoskeletal, Connective Tissue and Bone Disorders. Skin reactions and allergic reactions were also observed. Overall the serious adverse events and severe adverse events observed with celecoxib represented events seen in this patient population and events known to be associated with other NSAIDs.

Review of post-marketing spontaneous adverse event reports are of limited value in assessing the safety of celecoxib in children since celecoxib is not approved in pediatric patients. The Office of Surveillance and Epidemiology (OSE) found 30 adverse event reports in the AERS database from children treated off-label with celecoxib. Review of these cases did not uncover any new safety signals associated with celecoxib.

In the JRA population, physicians currently prescribe a variety of different NSAID products, including ibuprofen, naproxen, meloxicam and indomethacin. All of these products are associated with potentially serious adverse events. The most serious AEs seen with this class of products are potentially life-threatening GI bleeding and cardiovascular (CV) events. The COX-2 selective NSAIDs were developed in an effort to reduce the risk of serious GI toxicity. While it is widely believed that COX-2 selective NSAIDs have better GI tolerability, data have not clearly demonstrated that as a class COX-2 selective agents have a reduced incidence of serious GI toxicity. Although the COX-2 selective agents celecoxib, rofecoxib and valdecoxib have been shown to reduce the incidence of GI ulcers observed at endoscopy, GI ulcers have not been shown to predict GI bleeding in clinical trials. For example, in the CLASS trial that compared celecoxib with ibuprofen and diclofenac no difference was seen between study arms in the rate of serious GI bleeding. While clinical trial data comparing rofecoxib to naproxen demonstrated a reduced risk of GI bleeding for that agent, data are not available from clinical trials to confirm a reduced risk of GI bleeding for other COX-2 selective agents, including celecoxib. As discussed above in the trial of celecoxib in JRA, GI adverse events were seen at a similar rate in the celecoxib 6 mg/kg/d arm as with naproxen and serious GI events were more frequent in the celecoxib 6 mg/kg/d arm.

Other serious AEs seen with NSAIDs include fluid retention, edema, renal toxicity, hepatic enzyme elevation and bronchospasm in patients with aspirin-sensitive asthma. Of these, fluid retention and edema were not observed in the celecoxib trial in JRA. Liver enzyme elevation was observed in one 4-year-old child receiving celecoxib 6 mg/kg/d leading to withdrawal. One 6-year-old JRA patient in the celecoxib 6 mg/kg/d study arm developed a severe exacerbation of asthma 4 hours after the initial dose of celecoxib. In summary, a variety of AEs associated with NSAIDs as a class were seen in the JRA trial of celecoxib. Overall the data did not indicate that these AEs occurred at a rate that was clearly higher than that observed with the active comparator naproxen.

Recent findings from randomized clinical trials and epidemiologic studies have raised serious questions about the risks of cardiovascular (CV) adverse events in adult patients receiving COX-2 selective and non-selective NSAIDs. This increased risk was not appreciated initially, in part because myocardial infarctions and other thromboembolic events are not uncommon in the patient populations with osteoarthritis and rheumatoid arthritis studied in many clinical trials. No thromboembolic CVadverse events were seen

in the celecoxib study of JRA patients but it is nonetheless critical to consider the CV risk that children would have if they receive celecoxib or other NSAIDs long-term.

The data indicating an increased CV risk of NSAIDs are reviewed in detail elsewhere in other documents included in this briefing packet. In brief, placebo-controlled data are available with the COX-2 selective agents rofecoxib and celecoxib indicating an elevated risk of thromboembolic CV events. Clinical trial data with rofecoxib have shown an increased rate of serious adverse CV events compared to placebo (APPROVe trial) and compared to naproxen (VIGOR trial). The strongest data supporting an increased risk of CV adverse events comes from the NCI's Adenoma Prevention with Celecoxib (APC trial) which showed a dose-dependent 2-3 fold increased risk of CV adverse events compared to placebo after a mean duration of treatment of 33 months using the composite endpoint of death from CV causes, myocardial infarction or stroke.

Given the evidence of a CV risk of the COX-2 selective agents, how does that risk compare to the risk with COX-2 non-selective agents? Unfortunately, the absolute CV risk of non-selective NSAIDs is uncertain because long-term, placebo-controlled studies of these agents are generally not available. However, apart from some studies suggesting a lower CV risk with naproxen (e.g., VIGOR) data from long-term comparative studies with other COX-2 non-selective agents do not clearly show a lower rate of CV risk with COX-2 non-selective agents than with COX-2 selective agents. For example, a long-term study (CLASS) comparing celecoxib with ibuprofen and diclofenac showed no differences in CV adverse events. Observational studies have also not consistently shown a higher risk of CV events with COX-2 selective agents than with non-selective agents, with the possible exception of rofecoxib 50 mg, where a signal of increased CV risk was seen in two studies.

In summary, randomized controlled trial data have demonstrated an increased cardiovascular risk with the two COX-2 selective agents celecoxib and rofecoxib. Comparative trial data and observational studies have not clearly shown that the risk is lower with COX-2 non-selective agents. Taken together these data suggest that the risk of CV adverse events with COX-2 selective agents and COX-2 non-selective agents are in fact similar. Since children are at low risk of thromboembolic cardiovascular events short-term use of celecoxib or other NSAIDs is unlikely to confer an appreciable risk. However, because of the chronic nature of the disease JRA and its natural history many children are likely to receive these agents indefinitely and the risks conferred by many years of treatment are unknown.

In conclusion, assessing the risk-benefit relationship for celecoxib in JRA requires a careful consideration of the evidence of clinical benefits and risks of celecoxib and the risks and benefits of alternative NSAIDs used in JRA. Data are available to assess the short-term risks of celecoxib based on the clinical trials results in JRA up to 6 months and from information on risks of other agents in the NSAID class. However evidence is not available to estimate the long-term cardiovascular risk to children receiving celecoxib in view of the evidence of cardiovascular risk in adults. The uncertainty regarding cardiovascular risk poses a special challenge in weighing the evidence of risks and benefits of celecoxib use in JRA.

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 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 ratio[3] 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 exits 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.

<u>NSAIDs as a class</u>

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 heath 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.

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

PID#: A060340

DATE: August 30, 2006

FROM: Laura A. Governale, Pharm.D., MBA / Drug Use Data Specialist Team Leader
Division of Surveillance, Research and Communication Support
Office of Surveillance and Epidemiology

THROUGH: Solomon Iyasu, MD, MPH, Director
Division of Surveillance, Research and Communication Support
Office of Surveillance and Epidemiology

TO: Carolyn Yancy MD, Medical Officer
Division of Anesthesia, Analgesia, and Rheumatology Products

SUBJECT: Pediatric drug use review for Celebrex® (celecoxib); NDA 20-998/S-021

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

Background:

In response to a request for drug use data by the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP), this consult examines the utilization of Celebrex® (celecoxib), NDA 20-998, in the pediatric population, ages 0-18 years.

Celebrex® is currently not indicated for use in the pediatric population. DAARP has requested this consult in preparation for an upcoming Advisory Committee meeting on November 29, 2006, to discuss the efficacy supplement for Celebrex® (celecoxib), NDA 20-998/S-021, in the pediatric population, ages 2-18 years, for the treatment of Juvenile Rheumatoid Arthritis (JRA). Currently, Celebrex® has the following indications:

1. For relief of the signs and symptoms of osteoarthritis.
2. For relief of the signs and symptoms of rheumatoid arthritis in adults.
3. For the relief of signs and symptoms of ankylosing spondylitis.
4. For the management of acute pain in adults.
5. For the treatment of primary dysmenorrhea.
6. To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery).

This consult provides analyses of the distribution channels for Celebrex®, the numbers of prescriptions dispensed (by patient age and by prescribing physician specialty) and the number of unique patients who have received a prescription for Celebrex® from retail pharmacies from year 2002 through June 2006.

Memo:

Wholesale Sales Distribution

The IMS Health, IMS National Sales Perspectives™ measures the distribution of pharmaceutical products from manufacturers into the retail and non-retail markets. The majority of sales for Celebrex® (celecoxib) was distributed to retail channels which accounted for approximately 65% of the estimated 674 million capsules of product sold during July 2005 – June 2006[1]. The retail channels include chain pharmacies, independents, food stores with pharmacies, and mass merchandisers with pharmacies. The mail service channel accounted for approximately 26% of sales distribution and the non-retail channels accounted for approximately 9% of sales distribution.

Outpatient Dispensing Volume and Patient Demographics

Outpatient Dispensing: Prescription Counts and Physician Specialty

Verispan's VONA measures nationally projected outpatient prescriptions dispensed through retail pharmacies, excluding mail order pharmacies. Since year 2002, the number of dispensed prescriptions for pediatric patients has decrease by almost two-thirds from 112,000 (95% CI 111,000-113,000) prescriptions to 41,000 (95% CI 40,500 – 41,500) prescriptions by year 2005 (Table 1). The most dramatic decline in use was noted between year 2004 and 2005 where the number of dispensed prescriptions decreased by half from 80,000 (95% CI 79,400 – 80,600) to 41,000 (95% CI 40,500 – 41,500). Similar decline in use were observed for adults. Throughout this time period, less than 1% of all dispensed prescriptions for Celebrex® were for pediatric patients age 0-18 years.

Table 1. Total Retail Prescriptions Dispensed (in thousands) for Celebrex® by Age (0-18, 19+) From Year 2002 – June 2006.

	2002		2003		2004		2005		Jan-Jun 2006	
	TRxs (000)	***Share %***	**TRxs (000)**	***Share %***	**TRxs (000)**	***Share %***	**TRxs (000)**	***Share %***	**TRxs (000)**	***Share %***
Celebrex® (celecoxib)	21,234	*100.0%*	18,882	*100.0%*	19,038	*100.0%*	10,965	*100.0%*	5,520	*100.0%*
0-18	112	*0.5%*	88	*0.5%*	80	*0.4%*	41	*0.4%*	20	*0.4%*
19+	21,032	*99.0%*	18,704	*99.1%*	18,806	*98.8%*	10,825	*98.7%*	5,482	*99.3%*
UNSPEC.	90	*0.4%*	90	*0.5%*	152	*0.8%*	99	*0.9%*	19	*0.3%*

Verispan Vector One® : National, Years 2002 – June 2006, Extracted 8-25-2006; VONA Governale 8-25-06 A060304 Celebrex PdIT TRxAg.xls

[1] IMS Health, IMS National Sales Perspectives™, July 2005 – June 2006, Extracted 8-25-06. Original file: 0608cele.dvr

Physician Specialty

General Practice specialty was the most common physician specialty associated with a dispensed prescription for Celebrex®, accounting for approximately 30% of dispensing during the entire study period (Table 2). The Internal Medicine specialty was next in ranking and accounted for over 25% of dispensed prescriptions. Pediatricians ranked 13th in relation to all other specialties, accounting for less than 1% of all prescriptions dispensed for Celebrex® from year 2002 through June 2006.

Table 2. Total Retail Prescriptions Dispensed for Celebrex® (celecoxib) in Thousands by Physician Specialty, from Year 2002 to June 2006.

		2002		2003		2004		2005		Jan-Jun 2006	
		TRxs	***Share***	**TRxs**	***Share***	**TRxs**	***Share***	**TRxs**	***Share***	**TRxs**	***Share***
		(000)		**(000)**	***%***	**(000)**	***%***	**(000)**	***%***	**(000)**	***%***
Celecoxib		21,234	*100.0%*	18,882	*100.0%*	19,038	*100.0%*	10,965	*100.0%*	5,520	*100.0%*
1	**General practice***	6,654	*31.3%*	6,030	*31.9%*	6,009	*31.6%*	3,720	*33.9%*	1,919	*34.8%*
2	**IM**	5,337	*25.1%*	4,905	*26.0%*	4,898	*25.7%*	2,790	*25.4%*	1,407	*25.5%*
3	**ORTH SURG**	2,078	*9.8%*	1,699	*9.0%*	1,613	*8.5%*	913	*8.3%*	513	*9.3%*
4	**RHEUM**	1,058	*5.0%*	890	*4.7%*	843	*4.4%*	599	*5.5%*	309	*5.6%*
5	**UNSPEC**	2,005	*9.4%*	1,617	*8.6%*	1,933	*10.2%*	882	*8.0%*	246	*4.5%*
…	**All Others**	3,932	*18.5%*	3,583	*19.0%*	3,577	*18.8%*	1,969	*18.0%*	1,077	*19.5%*
13	**PED**	171	*0.8%*	161	*0.9%*	165	*0.9%*	92	*0.8%*	48	*0.9%*

*General Practice includes general practice, Family Medicine, Doctors of Osteopathy
Verispan Vector One® : National, Years 2002 – June 2006, Extracted 8-25-2006; VONA Governale 8-25-06 A060304 Celebrex PdIT MD.xls

When we looked at drug use mentions as reported by office-based physician practices, the majority of drug occurrences for Celebrex® in the pediatric population (age 0-18) were reported by the Orthopedic Surgery specialty, which accounted for approximately 66% of drug occurrences for the combined time period of year 2002 through June 2006 (Table 3). Drug occurrences reported by Rheumatologists accounted for less than 10% of mentions for the pediatric population during this time period.

Table 3. Total Number of Drug Occurrences as Reported by Office-Based Physician Practices for Celebrex® from Years 2002 through June 2006 Combined.

Celebrex®	Drug Occurrences (000)	*Share %*
Patient Age 0-18	1,266	*100.0%*
ORTH SURG	842	*66.5%*
GP/FM/DO	172	*13.6%*
RHEUM	116	*9.2%*
POD	35	*2.8%*
EM	10	*0.8%*
PED	33	*2.6%*
OB/GYN	16	*1.3%*
IM	21	*1.7%*
ENT	3	*0.2%*
UROL	6	*0.5%*
GEN SURG	6	*0.5%*
AO SURG	6	*0.5%*

Outpatient Dispensing: Patient Counts

Verispan's Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients receiving prescriptions dispensed through outpatient retail pharmacies. Patient counts were obtained from year 2002 to June 2006 for the dispensing of Celebrex®. The proportion of patients in each age band (Table 4) is similar to the proportions of prescriptions in each age band (Table 1). Pediatric patients accounted for 1% or less than 1% of all patients who received a prescription for Celebrex®. Similar to dispensed prescription data, the number of patients receiving a prescription for Celebrex® also decreased dramatically between year 2004 and 2005.

Table 4: Patients Receiving a Prescription for Celebrex® (celecoxib) from Outpatient Retail Pharmacies by Patient Age, Years 2002 - June 2006.

	Year 2002		**Year 2003**		**Year 2004**		**Year 2005**		**Jan-Jun 2006**	
	Projected Patient Count	*Total Patient Share*	Projected Patient Count	*Total Patient Share*	Projected Patient Count	*Total Patient Share*	Projected Patient Count	*Total Patient Share*	Projected Patient Count	*Total Patient Share*
Product Total	**6,632,610**		**5,966,299**		**5,966,074**		**3,214,208**		**2,228,823**	
0 – 18 Years	68,302	*1.03%*	54,480	*0.91%*	52,227	*0.88%*	22,436	*0.70%*	12,481	*0.56%*
19+ Years	6,552,694	*98.80%*	5,868,901	*98.37%*	5,834,131	*97.79%*	3,150,827	*98.03%*	2,208,836	*99.10%*
Unknown Age	54,099	*0.82%*	110,446	*1.85%*	164,236	*2.75%*	91,309	*2.84%*	19,770	*88.80%*

Verispan Vector One: Total Patient Tracker (TPT) Data Extracted 8-2006; TPT A060340 8-23-06 COX2s.xls,
*Due to aging of patients during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts.
**Subtotals may not sum exactly, due to rounding error.

Indications for use

Verispan's PDDA is a national survey which measures the indication for use of drug products mentioned during patient visits to office based physicians. Sprains of ankle and foot (ICD-9 845), and Osteocondropathies (ICD-9 732) were the two most commonly mentioned diagnoses associated with Celebrex® in the pediatric population during year 2004 and 2005[2]. Due to the survey's small sample size and the relatively low usage of Celebrex® in this population, a consistent trend could not be identified for any specific diagnosis during this analysis period. However, when all sprain injuries were combined, the totality of sprain injuries appeared to be the most common grouped diagnosis for the entire analysis period[†].

Conclusion

Less than 1% of total dispensed prescriptions for Celebrex® are for the pediatric population, ages 0-18, during years 2002 through June 2006. Similarly, the number of pediatric patients receiving a prescription for Celebrex® were less than 1% of the total during this time period. According to dispensed prescriptions, the majority of prescribing for Celebrex® were by General Practice and Internal Medicine specialties. According to office-based physician surveys, Orthopedic Surgeons appear to be the most common prescriber for Celebrex® to the pediatric population. The most common diagnoses associated with Celebrex® are for sprains and injuries.

[2] Verispan, PDDA, Years 2002 – June 2006, Extracted 8-25-06; PDDA A060340 8-25-06 Celebrex AgDx3.xls.
[†]Sprain of ankle and foot (ICD-9 845) and Spring of knee and leg (ICD-9 844) combined

DATA SOURCES

This review describes the annual sales and drug use patterns of Dovonex® with an emphasis on use in the pediatric population (ages 0 through 17 years). Proprietary drug use databases licensed by the Agency were used to conduct this analysis. The data sources for this analysis are described in detail below.

Outpatient Drug Usage

IMS HEALTH
IMS National Sales Perspectives™

IMS Health National Sales Perspectives™ measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into retail and non-retail markets. The volume of drug products transferred to these markets is expressed in terms of sales dollars, vials, and market share. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. These data are based on national projections.

VERISPAN, LLC
Vector One®: National (VONA)

Verispan's VONA is a nationally projected database which measures the retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One®database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2 billion prescription claims yearly, representing over 160 million unique patients.

The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores. Mail order prescriptions are not included in the sample at this time.

VERISPAN, LLC
Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, physician offices and hospitals. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million unique patients tracked across time.

VERISPAN, LLC
Physician Drug & Diagnosis Audit (PDDA)

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey that monitors disease states and the physician intended prescribing habits on a national-level. The survey is designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The audit is composed of approximately 3,100 office-based physicians representing 29 specialties

across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

The term drug uses refers to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a drug use does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Laura Governale
9/1/2006 09:13:47 AM
DRUG SAFETY OFFICE REVIEWER

Solomon Iyasu
9/5/2006 03:28:47 PM
MEDICAL OFFICER

CELEBREX®
celecoxib capsules

Cardiovascular Risk

- CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see **WARNINGS** and **CLINICAL TRIALS).**

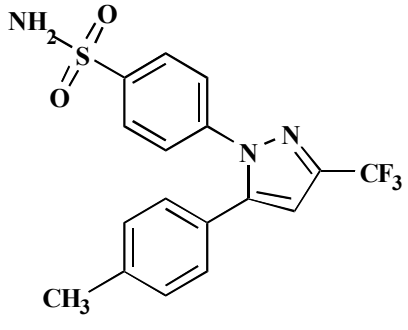
- CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Gastrointestinal Risk

- NSAIDs, including CELEBREX, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see **WARNINGS**).

DESCRIPTION

CELEBREX (celecoxib) is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. It has the following chemical structure:



The empirical formula for celecoxib is $C_{17}H_{14}F_3N_3O_2S$, and the molecular weight is 381.38.

CELEBREX oral capsules contain either 100 mg, 200 mg or 400 mg of celecoxib.

The inactive ingredients in CELEBREX capsules include: croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, sodium lauryl sulfate and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

CELEBREX is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of CELEBREX is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans, CELEBREX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. In animal colon tumor models, celecoxib reduced the incidence and multiplicity of tumors.

Platelets

In clinical trials using normal volunteers, CELEBREX at single doses up to 800 mg and multiple doses of 600 mg twice daily for up to 7 days duration (higher than recommended therapeutic doses) had no effect on reduction of platelet aggregation or increase in bleeding time. Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis. It is not known if there are any effects of CELEBREX on platelets that may contribute to the increased risk of serious cardiovascular thrombotic adverse events associated with the use of CELEBREX.

Fluid Retention

Inhibition of PGE2 synthesis may lead to sodium and water retention through increased reabsorption in the renal medullary thick ascending loop of Henle and perhaps other segments of the distal nephron. In the collecting ducts, PGE2 appears to inhibit water reabsorption by counteracting the action of antidiuretic hormone.

Pharmacokinetics

Absorption

Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Under fasting conditions, both peak plasma levels (C_{max}) and area under the curve (AUC) are roughly dose proportional up to 200 mg BID; at higher doses there are less than proportional increases in C_{max} and AUC (see Food Effects). Absolute bioavailability studies have not been conducted. With multiple dosing, steady state conditions are reached on or before Day 5.

The pharmacokinetic parameters of celecoxib in a group of healthy subjects are shown in Table 1.

Table 1
Summary of Single Dose (200 mg) Disposition
Kinetics of Celecoxib in Healthy Subjects[1]

Mean (%CV) PK Parameter Values				
C_{max}, ng/mL	**T_{max}, hr**	**Effective $t_{1/2}$, hr**	**V_{ss}/F, L**	**CL/F, L/hr**
705 (38)	2.8 (37)	11.2 (31)	429 (34)	27.7 (28)

[1]Subjects under fasting conditions (n=36, 19-52 yrs.)

Food Effects

When CELEBREX capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. Coadministration of CELEBREX with an aluminum- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in C_{max} and 10% in AUC. CELEBREX, at doses up to 200 mg

BID can be administered without regard to timing of meals. Higher doses (400 mg BID) should be administered with food to improve absorption.

Distribution

In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. *In vitro* studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, α_1-acid glycoprotein. The apparent volume of distribution at steady state (V_{ss}/F) is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Metabolism

Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors. Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Excretion

Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($t_{1/2}$) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Special Populations

Geriatric

At steady state, elderly subjects (over 65 years old) had a 40% higher C_{max} and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib C_{max} and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary. However, for patients of less than 50 kg in body weight, initiate therapy at the lowest recommended dose.

Pediatric

CELEBREX capsules have not been investigated in pediatric patients below 18 years of age.

Race

Meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this finding is unknown.

Hepatic Insufficiency

A pharmacokinetic study in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment has shown that steady-state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore, the daily recommended dose of

CELEBREX capsules should be reduced by approximately 50% in patients with moderate (Child-Pugh Class B) hepatic impairment. Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of CELEBREX in patients with severe hepatic impairment is not recommended (see **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency
In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied. Similar to other NSAIDs, CELEBREX is not recommended in patients with severe renal insufficiency (see **WARNINGS – Advanced Renal Disease**).

Drug Interactions
Also see **PRECAUTIONS – Drug Interactions.**

General
Significant interactions may occur when celecoxib is administered together with drugs that inhibit P450 2C9. *In vitro* studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4.

Clinical studies with celecoxib have identified potentially significant interactions with fluconazole and lithium. Experience with nonsteroidal anti-inflammatory drugs (NSAIDs) suggests the potential for interactions with furosemide and ACE inhibitors. The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole, methotrexate, phenytoin, and tolbutamide have been studied *in vivo* and clinically important interactions have not been found.

CLINICAL STUDIES

Osteoarthritis (OA)
CELEBREX has demonstrated significant reduction in joint pain compared to placebo. CELEBREX was evaluated for treatment of the signs and the symptoms of OA of the knee and hip in placebo- and active-controlled clinical trials of up to 12 weeks duration. In patients with OA, treatment with CELEBREX 100 mg BID or 200 mg QD resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, CELEBREX doses of 100 mg BID and 200 mg BID provided significant reduction of pain within 24-48 hours of initiation of dosing. At doses of 100 mg BID or 200 mg BID the effectiveness of CELEBREX was shown to be similar to that of naproxen 500 mg BID. Doses of 200 mg BID provided no additional benefit above that seen with 100 mg BID. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg BID or 200 mg QD.

Rheumatoid Arthritis (RA)
CELEBREX has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. CELEBREX was evaluated for treatment of the signs and symptoms of RA in placebo- and active-controlled clinical trials of up to 24 weeks in duration. CELEBREX was shown to be superior to placebo in these studies, using the ACR20 Responder Index, a composite of clinical, laboratory, and

functional measures in RA. CELEBREX doses of 100 mg BID and 200 mg BID were similar in effectiveness and both were comparable to naproxen 500 mg BID.

Although CELEBREX 100 mg BID and 200 mg BID provided similar overall effectiveness, some patients derived additional benefit from the 200 mg BID dose. Doses of 400 mg BID provided no additional benefit above that seen with 100-200 mg BID.

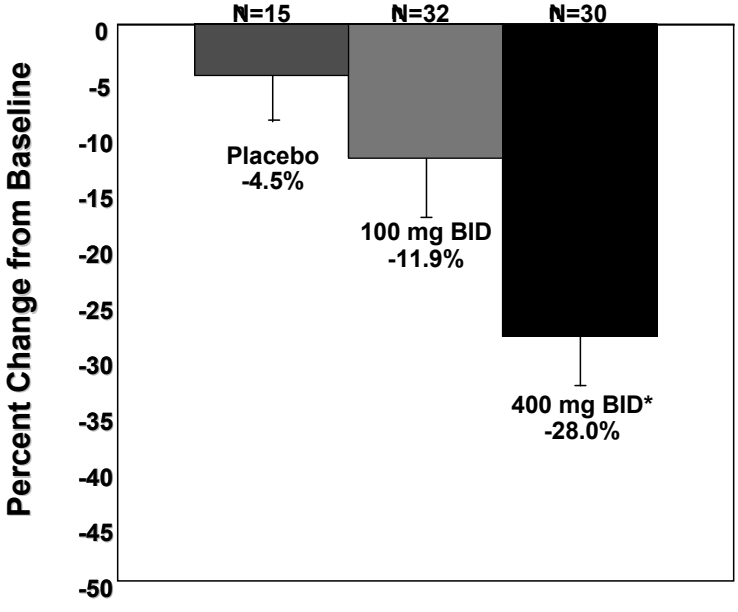
Analgesia, including primary dysmenorrhea
In acute analgesic models of post-oral surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea, CELEBREX relieved pain that was rated by patients as moderate to severe. Single doses (see **DOSAGE AND ADMINISTRATION**) of CELEBREX provided pain relief within 60 minutes.

Ankylosing Spondylitis (AS)
CELEBREX was evaluated in AS patients in two placebo- and active-controlled clinical trials of 6 and 12 weeks duration. CELEBREX at doses of 100 mg BID, 200 mg QD and 400 mg QD was shown to be statistically superior to placebo in these studies for all three co-primary efficacy measures assessing global pain intensity (Visual Analogue Scale), global disease activity (Visual Analogue Scale) and functional impairment (Bath Ankylosing Spondylitis Functional Index). In the 12-week study, there was no difference in the extent of improvement between the 200 mg and 400 mg celecoxib doses in a comparison of mean change from baseline, but there was a greater percentage of patients who responded to celecoxib 400 mg, 53%, than to celecoxib 200 mg, 44%, using the Assessment in Ankylosing Spondylitis response criteria (ASAS 20). The ASAS 20 defines a responder as improvement from baseline of at least 20% and an absolute improvement of at least 10 mm, on a 0 to 100 mm scale, in at least three of the four following domains: patient global, pain, Bath Ankylosing Spondylitis Functional Index, and inflammation. The responder analysis also demonstrated no change in the responder rates beyond 6 weeks.

Familial Adenomatous Polyposis (FAP)
CELEBREX was evaluated to reduce the number of adenomatous colorectal polyps. A randomized double-blind placebo-controlled study was conducted in patients with FAP. The study population included 58 patients with a prior subtotal or total colectomy and 25 patients with an intact colon. Thirteen patients had the attenuated FAP phenotype.

One area in the rectum and up to four areas in the colon were identified at baseline for specific follow-up, and polyps were counted at baseline and following six months of treatment. The mean reduction in the number of colorectal polyps was 28% for CELEBREX 400 mg BID, 12% for CELEBREX 100 mg BID and 5% for placebo. The reduction in polyps observed with CELEBREX 400 mg BID was statistically superior to placebo at the six-month timepoint (p=0.003). (See Figure 1)

Figure 1
Percent Change from Baseline in Number of Colorectal Polyps (FAP Patients)



*** p=0.003 versus placebo**

Special Studies

Celecoxib Long-Term Arthritis Safety Study (CLASS)

The Celecoxib Long-Term Arthritis Safety Study (CLASS) was a prospective long-term safety outcome study conducted postmarketing in approximately 5,800 OA patients and 2,200 RA patients. Patients received CELEBREX 400 mg BID (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP), ibuprofen 800 mg TID or diclofenac 75 mg BID (common therapeutic doses). Median exposures for CELEBREX (n = 3,987) and diclofenac (n = 1,996) were 9 months while ibuprofen (n = 1,985) was 6 months. The primary endpoint of this outcome study was the incidence of *complicated ulcers* (gastrointestinal bleeding, perforation or obstruction). Patients were allowed to take concomitant low-dose (≤ 325 mg/day) aspirin (ASA) for cardiovascular prophylaxis (ASA subgroups: CELEBREX, n = 882; diclofenac, n = 445; ibuprofen, n = 412). Differences in the incidence of *complicated ulcers* between CELEBREX and the combined group of ibuprofen and diclofenac were not statistically significant.

Those patients on CELEBREX and concomitant low-dose ASA (N=882) experienced 4-fold higher rates of *complicated ulcers* compared to those not on ASA (N=3105). The Kaplan-Meier rate for complicated ulcers at 9 months was 1.12% versus 0.32% for those on low dose ASA and those not on ASA, respectively (see **WARNINGS — Gastrointestinal (GI) Effects– Risk of GI Ulceration, Bleeding, and Perforation**).

The estimated cumulative rates at 9 months of *complicated and symptomatic ulcers* for patients treated with CELEBREX 400 mg BID are described in Table 2. Table 2 also displays results for patients less

than or greater than 65 years of age. The difference in rates between CELEBREX alone and CELEBREX with ASA groups may be due to the higher risk for GI events in ASA users.

Table 2
***Complicated and Symptomatic Ulcer* Rates in Patients Taking CELEBREX 400 mg BID (Kaplan-Meier Rates at 9 months [%]) Based on Risk Factors**

	***Complicated and Symptomatic Ulcer* Rates**
All Patients	
CELEBREX alone (n=3105)	0.78
CELEBREX with ASA (n=882)	2.19
Patients <65 Years	
CELEBREX alone (n=2025)	0.47
CELEBREX with ASA (n=403)	1.26
Patients ≥65 Years	
CELEBREX alone (n=1080)	1.40
CELEBREX with ASA (n=479)	3.06

In a small number of patients with a history of ulcer disease, the *complicated and symptomatic ulcer* rates in patients taking CELEBREX alone or CELEBREX with ASA were, respectively, 2.56% (n=243) and 6.85% (n=91) at 48 weeks. These results are to be expected in patients with a prior history of ulcer disease (see **WARNINGS – Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation** and **Safety Data from CLASS Study:**
Hematological Events

Cardiovascular safety outcomes were also evaluated in the CLASS trial. Kaplan-Meier cumulative rates for investigator-reported serious cardiovascular thromboembolic adverse events (including MI, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischemic attacks, and ischemic cerebrovascular accidents) demonstrated no differences between the CELEBREX, diclofenac, or ibuprofen treatment groups. The cumulative rates in all patients at nine months for CELEBREX, diclofenac, and ibuprofen were 1.2%, 1.4%, and 1.1%, respectively. The cumulative rates in non-ASA users at nine months in each of the three treatment groups were less than 1%. The cumulative rates for myocardial infarction in non-ASA users at nine months in each of the three treatment groups were less than 0.2%. There was no placebo group in the CLASS trial, which limits the ability to determine whether the three drugs tested had no increased risk of CV events or if they all increased the risk to a similar degree.

Adenomatous Polyp Prevention Studies
Cardiovascular safety was evaluated in two randomized, double-blind, placebo-controlled, three-year studies involving patients with Sporadic Adenomatous Polyps treated with CELEBREX. The first of these studies was the APC (Prevention of Sporadic Colorectal Adenomas with Celecoxib) study which compared CELEBREX 400 mg twice daily (N=671) and CELEBREX 200 mg twice daily (N=685) to placebo (N=679). Preliminary safety information from this trial demonstrated a dose-related increase in serious cardiovascular events (mainly myocardial infarction [MI]) at CELEBREX doses of 200 mg

and 400 mg twice daily compared to placebo). The cumulative rates of serious cardiovascular thrombotic events began to differ between the CELEBREX treatment groups and placebo after approximately one year of treatment. There were 2.8 to 3.1 years of follow-up in the APC trial except those patients who died earlier. The relative risk (RR) for the composite endpoint of cardiovascular death, MI, or stroke was 3.4 (95% CI 1.4 – 8.5) for the higher dose and 2.5 (95% CI 1.0 – 6.4) for the lower dose of CELEBREX compared to placebo. The absolute risk for the composite endpoint was 3.0% for the higher dose of CELEBREX, 2.2% for the lower dose of CELEBREX, and 0.9% for placebo.

The second long-term study, PreSAP (Prevention of Colorectal Sporadic Adenomatous Polyps) compared CELEBREX 400 mg once daily to placebo. Preliminary safety information from this trial demonstrated no increased cardiovascular risk for the composite endpoint of cardiovascular death, MI or stroke. The reason for the differing results for CV events in the APC and PreSAP trials is not known.

Clinical trials of other COX-2 selective and nonselective NSAIDs of up to three-year duration have shown an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. As a result, all NSAIDs are considered potentially associated with this risk.

Endoscopic Studies

The correlation between findings of short-term endoscopic studies with CELEBREX and the relative incidence of clinically significant serious upper GI events with long-term use has not been established.

A randomized, double-blind study in 430 RA patients was conducted in which an endoscopic examination was performed at 6 months. The incidence of endoscopic ulcers in patients taking CELEBREX 200 mg twice daily was 4% vs. 15% for patients taking diclofenac SR 75 mg twice daily. However, CELEBREX was not statistically different than diclofenac for clinically relevant GI outcomes in the CLASS trial (see **Special Studies-*CLASS***).

The incidence of endoscopic ulcers was studied in two 12-week, placebo-controlled studies in 2157 OA and RA patients in whom baseline endoscopies revealed no ulcers. There was no dose relationship for the incidence of gastroduodenal ulcers and the dose of CELEBREX (50 mg to 400 mg twice daily). The incidence for naproxen 500 mg twice daily was 16.2 and 17.6% in the two studies, for placebo was 2.0 and 2.3%, and for all doses of CELEBREX the incidence ranged between 2.7%-5.9%. There have been no large, clinical outcome studies to compare clinically relevant GI outcomes with CELEBREX and naproxen.

In the endoscopic studies, approximately 11% of patients were taking aspirin (≤ 325 mg/day). In the CELEBREX groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than the endoscopic ulcer rates observed in the active comparator groups, with or without aspirin.

Serious clinically significant upper GI bleeding has been observed in patients receiving CELEBREX in controlled and open-labeled trials (see **Special Studies - *CLASS*** and **WARNINGS – Gastrointestinal (GI) Effects– Risk of GI Ulceration, Bleeding, and Perforation**).

INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of CELEBREX and other treatment options before deciding to use CELEBREX. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

CELEBREX is indicated:

1) For relief of the signs and symptoms of osteoarthritis.

2) For relief of the signs and symptoms of rheumatoid arthritis in adults.

3) For the relief of signs and symptoms of ankylosing spondylitis.

4) For the management of acute pain in adults (see **CLINICAL STUDIES**).

5) For the treatment of primary dysmenorrhea.

6) To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery). It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients. It is also not known whether the effects of CELEBREX treatment will persist after CELEBREX is discontinued. The efficacy and safety of CELEBREX treatment in patients with FAP beyond six months have not been studied (see **CLINICAL STUDIES**, **WARNINGS** and **PRECAUTIONS** sections).

CONTRAINDICATIONS

CELEBREX is contraindicated in patients with known hypersensitivity to celecoxib.

CELEBREX should not be given to patients who have demonstrated allergic-type reactions to sulfonamides.

CELEBREX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see **WARNINGS — Anaphylactoid Reactions**, and **PRECAUTIONS — Preexisting Asthma**).

CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**)

WARNINGS

Cardiovascular Effects

Cardiovascular Thrombotic Events

Chronic use of CELEBREX may cause an increased risk of serious adverse cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. In the APC trial, the relative risk for the composite endpoint of cardiovascular death, MI, or stroke was 3.4 (95% CI 1.4 – 8.5) for CELEBREX

400 mg twice daily and 2.5 (95% CI 1.0 – 6.4) for the CELEBREX 200 mg twice daily compared to placebo (see **Special Studies – *Adenomatous Polyp Studies***)

All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with CELEBREX, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and CELEBREX does increase the risk of serious GI events (see **WARNINGS, Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation).**

Two large, controlled, clinical trials of a different COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see **CONTRAINDICATIONS**).

Hypertension
As with all NSAIDS, CELEBREX can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including CELEBREX, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with CELEBREX and throughout the course of therapy. The rates of hypertension from the CLASS trial in the CELEBREX, ibuprofen and diclofenac treated patients were 2.4%, 4.2% and 2.5%, respectively (see **Special Studies - *CLASS***).

Congestive Heart Failure and Edema
Fluid retention and edema have been observed in some patients taking NSAIDs, including CELEBREX (see **ADVERSE REACTIONS**). In the CLASS study (see **Special Studies – *CLASS***), the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on CELEBREX 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP), ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily were 4.5%, 6.9% and 4.7%, respectively. CELEBREX should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal (GI) Effects — Risk of GI Ulceration, Bleeding, and Perforation
NSAIDs, including CELEBREX, can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Complicated and symptomatic ulcer rates were 0.78% at nine months for all patients in the CLASS trial, and 2.19% for the subgroup on low dose ASA. Patients 65 years of age and older had an incidence of 1.40% at nine months, 3.06% when also taking ASA (see **Special Studies, *CLASS***). With longer duration of use of NSAIDs, there is a trend for increasing the likelihood of

developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. Physicians and patients should remain alert for signs and symptoms of GI ulceration and bleeding during CELEBREX therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with CELEBREX have shown renal effects similar to those observed with comparator NSAIDs.

Advanced Renal Disease
No information is available from controlled clinical studies regarding the use of CELEBREX in patients with advanced renal disease. Therefore, treatment with CELEBREX is not recommended in these patients with advanced renal disease. If CELEBREX therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions
As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to CELEBREX. In post-marketing experience, rare cases of anaphylactic reactions and angioedema have been reported in patients receiving CELEBREX. CELEBREX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see **CONTRAINDICATIONS** and **PRECAUTIONS — Preexisting Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions

CELEBREX is a sulfonamide and can cause serious skin adverse events such as exfoliative dermatitis, Stevens Johnson syndrome (SJS), and toxic epidermal necrolysis (TENS), which can be fatal. These serious events can occur without warning and in patients without prior known sulfa allergy. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy
In late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus (see **PRECAUTIONS – Pregnancy**).

Familial Adenomatous Polyposis (FAP): Treatment with CELEBREX in FAP has not been shown to reduce the risk of gastrointestinal cancer or the need for prophylactic colectomy or other FAP-related surgeries. Therefore, the usual care of FAP patients should not be altered because of the concurrent administration of CELEBREX. In particular, the frequency of routine endoscopic surveillance should not be decreased and prophylactic colectomy or other FAP-related surgeries should not be delayed.

PRECAUTIONS

General
CELEBREX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of CELEBREX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Hepatic Effects
Borderline elevations of one or more liver associated enzymes may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including CELEBREX (see **ADVERSE REACTIONS** – post-marketing experience). In controlled clinical trials of CELEBREX, the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of normal) of liver associated enzymes was 6% for CELEBREX and 5% for placebo, and approximately 0.2% of patients taking CELEBREX and 0.3% of patients taking placebo had notable elevations of ALT and AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with CELEBREX. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), CELEBREX should be discontinued.

Hematological Effects
Anemia is sometimes seen in patients receiving CELEBREX. In controlled clinical trials the incidence of anemia was 0.6% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. CELEBREX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages (see **CLINICAL PHARMACOLOGY—Platelets**).

Preexisting Asthma
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, CELEBREX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients
Patients should be informed of the following information before initiating therapy with CELEBREX and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. CELEBREX, like other NSAIDs, may cause serious CV side effects such as MI or stroke which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice if they observe any of these signs or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS - Cardiovascular Effects**).

2. CELEBREX, like other NSAIDs, can cause gastrointestinal discomfort and, rarely, more serious side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when they observe any signs or symptoms that are indicative of these disorders, including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS — Gastrointestinal (GI) Effects – Risk of Gastrointestinal Ulceration, Bleeding, and Perforation**).

3. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible. CELEBREX is a sulfonamide and can cause serious skin side effects such as exfoliative dermatitis, SJS, and TENS, which may result in hospitalizations and even death. These reactions can occur with all NSAIDs, even non-sulfonamides. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients with prior history of sulfa allergy should not take CELEBREX.

4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.

5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). Patients should be instructed that they should stop therapy and seek immediate medical therapy if these signs and symptoms occur.

6. Patients should be informed of the signs and symptoms of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). Patients should be instructed to seek immediate emergency assistance if they develop any of these signs and symptoms (see **WARNINGS – Anaphylactoid Reactions**).

7. Patients should be informed that in late pregnancy CELEBREX should be avoided because it may cause premature closure of the ductus arteriosus.

8. Patients with familial adenomatous polyposis (FAP) should be informed that CELEBREX has not been shown to reduce colorectal, duodenal or other FAP-related cancers, or the need for endoscopic surveillance, prophylactic or other FAP-related surgery. Therefore, all patients with FAP should be instructed to continue their usual care while receiving CELEBREX.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have a CBC and a chemistry profile checked periodically. If abnormal liver tests or renal tests persist or worsen, CELEBREX should be discontinued.

In controlled clinical trials, elevated BUN occurred more frequently in patients receiving CELEBREX compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

Drug Interactions

General

Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution.

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of cytochrome P450 2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by P450 2D6.

ACE-inhibitors

Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking CELEBREX concomitantly with ACE-inhibitors.

Aspirin
CELEBREX can be used with low-dose aspirin. However, concomitant administration of aspirin with CELEBREX increases the rate of GI ulceration or other complications, compared to use of CELEBREX alone (see **CLINICAL STUDIES — Special Studies — CLASS, WARNINGS – Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation**, **and WARNINGS – Cardiovascular Effects**).

Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis.

Fluconazole: Concomitant administration of fluconazole at 200 mg QD resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole (see **Pharmacokinetics — *Metabolism***). CELEBREX should be introduced at the lowest recommended dose in patients receiving fluconazole.

Furosemide
Clinical studies, as well as post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Lithium
In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg BID with CELEBREX 200 mg BID as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when CELEBREX is introduced or withdrawn.

Methotrexate
In an interaction study of rheumatoid arthritis patients taking methotrexate, CELEBREX did not have a significant effect on the pharmacokinetics of methotrexate.

Warfarin
Anticoagulant activity should be monitored, particularly in the first few days, after initiating or changing CELEBREX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of 2-5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, serious bleeding events, some of which were fatal, have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin.

Carcinogenesis, mutagenesis, impairment of fertility
Celecoxib was not carcinogenic in rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2- to 4-fold the human exposure as measured by the $AUC_{0\text{-}24}$ at 200 mg BID) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the $AUC_{0\ 24}$ at 200 mg BID) for two years.

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an *in vivo* micronucleus test in rat bone marrow.

Celecoxib did not impair male and female fertility in rats at oral doses up to 600 mg/kg/day (approximately 11-fold human exposure at 200 mg BID based on the AUC_{0-24}).

Pregnancy

Teratogenic effects

Pregnancy Category C. Celecoxib at oral doses ≥150 mg/kg/day (approximately 2-fold human exposure at 200 mg BID as measured by AUC_{0-24}), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥30 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg BID) throughout organogenesis. There are no studies in pregnant women. CELEBREX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects

Celecoxib produced pre-implantation and post-implantation losses and reduced embryo/fetal survival in rats at oral dosages ≥50 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg BID). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function, nor are they expected at clinical exposures. No studies have been conducted to evaluate the effect of celecoxib on the closure of the ductus arteriosus in humans. Therefore, use of CELEBREX during the third trimester of pregnancy should be avoided.

Labor and delivery

Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 7-fold human exposure as measured by the AUC_{0-24} at 200 mg BID). The effects of CELEBREX on labor and delivery in pregnant women are unknown.

Nursing mothers

Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. Limited data from one subject indicate that celecoxib is also excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CELEBREX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated.

Geriatric Use

Of the total number of patients who received CELEBREX in clinical trials, more than 3,300 were 65-74 years of age, while approximately 1,300 additional patients were 75 years and over. No substantial differences in effectiveness were observed between these subjects and younger subjects. In

clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers. However, as with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients (see **WARNINGS – Gastrointestinal (GI) Effects – Risk of GI Ulceration, Bleeding, and Perforation**).

ADVERSE REACTIONS

Of the CELEBREX treated patients in the premarketing controlled clinical trials, approximately 4,250 were patients with OA, approximately 2,100 were patients with RA, and approximately 1,050 were patients with post-surgical pain. More than 8,500 patients have received a total daily dose of CELEBREX of 200 mg (100 mg BID or 200 mg QD) or more, including more than 400 treated at 800 mg (400 mg BID). Approximately 3,900 patients have received CELEBREX at these doses for 6 months or more; approximately 2,300 of these have received it for 1 year or more and 124 of these have received it for 2 years or more.

Adverse events from CELEBREX premarketing controlled arthritis trials

Table 3 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving CELEBREX from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group. Since these 12 trials were of different durations, and patients in the trials may not have been exposed for the same duration of time, these percentages do not capture cumulative rates of occurrence.

Table 3

Adverse Events Occurring in ≥2% of CELEBREX Patients From CELEBREX Premarketing Controlled Arthritis Trials

	CELEBREX (100-200 mg BID or 200 mg QD) (n=4146)	**Placebo** (n=1864)	**Naproxen** 500 mg BID (n=1366)	**Diclofenac** 75 mg BID (n=387)	**Ibuprofen** 800 mg TID (n=345)
Gastrointestinal					
Abdominal pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a whole					
Back pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral edema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-accidental	2.9%	2.3%	3.0%	2.6%	3.2%
Central and peripheral nervous system					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory					
Pharyngitis	2.3%	1.1%	1.7%	1.6%	2.6%
Rhinitis	2.0%	1.3%	2.4%	2.3%	0.6%
Sinusitis	5.0%	4.3%	4.0%	5.4%	5.8%
Upper respiratory tract infection	8.1%	6.7%	9.9%	9.8%	9.9%

Skin					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving CELEBREX and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of CELEBREX patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

The following adverse events occurred in 0.1 - 1.9% of patients regardless of causality.

CELEBREX
(100 - 200 mg BID or 200 mg QD)

Gastrointestinal: Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, tooth disorder, vomiting

Cardiovascular: Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction

General: Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain

Resistance mechanism disorders: Herpes simplex, herpes zoster, infection bacterial, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media

Central, peripheral nervous system: Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, vertigo

Female reproductive: Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage, vaginitis

Male reproductive: Prostatic disorder

Hearing and vestibular: Deafness, ear abnormality, earache, tinnitus

Heart rate and rhythm: Palpitation, tachycardia

Liver and biliary system: Hepatic function abnormal, SGOT increased, SGPT increased

Metabolic and nutritional: BUN increased, CPK increased, diabetes mellitus, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weight increase

Musculoskeletal: Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis

Platelets (bleeding or clotting): Ecchymosis, epistaxis, thrombocythemia

Psychiatric: Anorexia, anxiety, appetite increased, depression, nervousness, somnolence

Hemic: Anemia

Respiratory: Bronchitis**,** bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia

Skin and appendages: Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria

Application site disorders:	Cellulitis, dermatitis contact, injection site reaction, skin nodule
Special senses:	Taste perversion
Urinary system:	Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus, urinary incontinence, urinary tract infection
Vision:	Blurred vision, cataract, conjunctivitis, eye pain, glaucoma

Other serious adverse reactions which occur rarely (estimated <0.1%), regardless of causality
The following serious adverse events have occurred rarely in patients taking CELEBREX. Cases reported only in the post-marketing experience are indicated in italics.

Cardiovascular:	Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, *vasculitis, deep venous thrombosis*
Gastrointestinal:	Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, ileus
Liver and biliary system:	Cholelithiasis, *hepatitis, jaundice, liver failure*
Hemic and lymphatic:	Thrombocytopenia, *agranulocytosis, aplastic anemia, pancytopenia, leukopenia*
Metabolic:	*Hypoglycemia, hyponatremia*
Nervous system:	*Aseptic meningitis,* ataxia, suicide, *ageusia, anosmia, fatal intracranial hemorrhage* (see PRECAUTIONS – Drug Interactions – *Warfarin*)
Renal:	Acute renal failure, *interstitial nephritis*
Skin:	*Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis*
General:	Sepsis, sudden death, *anaphylactoid reaction*, *angioedema*

Safety Data from CLASS Study

Hematological Events

During this study (see **Special Studies – *CLASS***), the incidence of clinically significant decreases in hemoglobin (>2 g/dL) confirmed by repeat testing was lower in patients on CELEBREX 400 mg BID (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP) compared to patients on either diclofenac 75 mg BID or ibuprofen 800 mg TID: 0.5%, 1.3% and 1.9%, respectively. The lower incidence of events with CELEBREX was maintained with or without ASA use (see **CLINICAL PHARMACOLOGY - Platelets**).

Withdrawals/Serious Adverse Events

Kaplan-Meier cumulative rates at 9 months for withdrawals due to adverse events for CELEBREX, diclofenac and ibuprofen were 24%, 29%, and 26%, respectively. Rates for serious adverse events (i.e., those causing hospitalization or felt to be life threatening or otherwise medically significant) regardless of causality were not different across treatment groups, respectively, 8%, 7%, and 8%.

Adverse events from ankylosing spondylitis studies: A total of 378 patients were treated with CELEBREX in placebo- and active- controlled ankylosing spondylitis studies. Doses up to 400 mg QD

were studied. The types of adverse events reported in the ankylosing spondylitis studies were similar to those reported in the arthritis studies.

Adverse events from analgesia and dysmenorrhea studies
Approximately 1,700 patients were treated with CELEBREX in analgesia and dysmenorrhea studies. All patients in post-oral surgery pain studies received a single dose of study medication. Doses up to 600 mg/day of CELEBREX were studied in primary dysmenorrhea and post-orthopedic surgery pain studies. The types of adverse events in the analgesia and dysmenorrhea studies were similar to those reported in arthritis studies. The only additional adverse event reported was post-dental extraction alveolar osteitis (dry socket) in the post-oral surgery pain studies.

Adverse events from the controlled trial in familial adenomatous polyposis
The adverse event profile reported for the 83 patients with familial adenomatous polyposis enrolled in the randomized, controlled clinical trial was similar to that reported for patients in the arthritis controlled trials. Intestinal anastomotic ulceration was the only new adverse event reported in the FAP trial, regardless of causality, and was observed in 3 of 58 patients (one at 100 mg BID, and two at 400 mg BID) who had prior intestinal surgery.

OVERDOSAGE

No overdoses of CELEBREX were reported during clinical trials. Doses up to 2400 mg/day for up to 10 days in 12 patients did not result in serious toxicity. Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. No information is available regarding the removal of celecoxib by hemodialysis, but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of CELEBREX and other treatment options before deciding to use CELEBREX. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

For osteoarthritis and rheumatoid arthritis, the lowest dose of CELEBREX should be sought for each patient. These doses can be given without regard to timing of meals.

Osteoarthritis
For relief of the signs and symptoms of osteoarthritis the recommended oral dose is 200 mg per day administered as a single dose or as 100 mg twice per day.

Rheumatoid arthritis
For relief of the signs and symptoms of rheumatoid arthritis the recommended oral dose is 100 to 200 mg twice per day.

Ankylosing Spondylitis (AS)
For the management of the signs and symptoms of AS, the recommended dose of CELEBREX is 200 mg daily single (once per day) or divided (twice per day) doses. If no effect is observed after 6 weeks, a trial of 400 mg daily may be worthwhile. If no effect is observed after 6 weeks on 400 mg daily, a response is not likely and consideration should be given to alternate treatment options.

Management of Acute Pain and Treatment of Primary Dysmenorrhea
The recommended dose of CELEBREX is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed.

Familial adenomatous polyposis (FAP)
Usual medical care for FAP patients should be continued while on CELEBREX. To reduce the number of adenomatous colorectal polyps in patients with FAP, the recommended oral dose is 400 mg twice per day to be taken with food.

Special Populations
Hepatic insufficiency
The daily recommended dose of CELEBREX capsules in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by approximately 50%. The use of CELEBREX in patients with severe hepatic impairment is not recommended (see **CLINICAL PHARMACOLOGY – Special Populations**).

HOW SUPPLIED

CELEBREX 100-mg capsules are white, reverse printed white on blue band of body and cap with markings of 7767 on the cap and 100 on the body, supplied as:

NDC Number	Size
0025-1520-31	bottle of 100
0025-1520-51	bottle of 500
0025-1520-34	carton of 100 unit dose

CELEBREX 200-mg capsules are white, with reverse printed white on gold band with markings of 7767 on the cap and 200 on the body, supplied as:

NDC Number	Size
0025-1525-31	bottle of 100
0025-1525-51	bottle of 500
0025-1525-34	carton of 100 unit dose

CELEBREX 400-mg capsules are white, with reverse printed white on green band with markings of 7767 on the cap and 400 on the body, supplied as:

NDC Number	Size
0025-1530-02	bottle of 60
0025-1530-01	carton of 100 unit dose

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Rx only Revised: July 2005

CELEBREX®
celecoxib capsules

LAB-0036-7.0

[Code of Federal Regulations]
[Title 21, Volume 1]
[Revised as of April 1, 2006]
[CITE: 21CFR50]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

SUBCHAPTER A--GENERAL

PART 50 PROTECTION OF HUMAN SUBJECTS

Subpart D--Additional Safeguards for Children in Clinical Investigations

Sec. 50.50 IRB duties.

In addition to other responsibilities assigned to IRBs under this part and part 56 of this chapter, each IRB must review clinical investigations involving children as subjects covered by this subpart D and approve only those clinical investigations that satisfy the criteria described in 50.51, 50.52, or 50.53 and the conditions of all other applicable sections of this subpart D.

Sec. 50.51 Clinical investigations not involving greater than minimal risk.

Any clinical investigation within the scope described in 50.1 and 56.101 of this chapter in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in 50.55.

Sec. 50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

Any clinical investigation within the scope described in 50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if the IRB finds and documents that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

Sec. 50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

Any clinical investigation within the scope described in 50.1 and56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds and documents that:

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

Sec. 50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

If an IRB does not believe that a clinical investigation within the scope described in 50.1 and 56.101 of this chapter and involving children as subjects meets the requirements of 50.51, 50.52, or 50.53, the clinical investigation may proceed only if:

(a) The IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:

(1) That the clinical investigation in fact satisfies the conditions of 50.51, 50.52, or 50.53, as applicable, or

(2) That the following conditions are met:

(i) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The clinical investigation will be conducted in accordance with sound ethical principles; and

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 50.55.

Sec. 50.55 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent.

(b) In determining whether children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate.

(c) The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines:

(1) That the capability of some or all of the children is so

limited that they cannot reasonably be consulted, or

(2) That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.

(d) Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that:

(1) The clinical investigation involves no more than minimal risk to the subjects;

(2) The waiver will not adversely affect the rights and welfare of the subjects;

(3) The clinical investigation could not practicably be carried out without the waiver; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that the permission of each child's parents or guardian is granted.

(1) Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient, if consistent with State law, for clinical investigations to be conducted under 50.51 or 50.52.

(2) Where clinical investigations are covered by 50.53 or 50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child if consistent with State law.

(f) Permission by parents or guardians must be documented in accordance with and to the extent required by 50.27.

(g) When the IRB determines that assent is required, it must also determine whether and how assent must be documented.

Sec. 50.56 Wards.

(a) Children who are wards of the State or any other agency, institution, or entity can be included in clinical investigations approved under 50.53 or 50.54 only if such clinical investigations are:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the clinical investigation is approved under paragraph (a) of this section, the IRB must require appointment of an advocate for each child who is a ward.

(1) The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

(2) One individual may serve as advocate for more than one child.

(3) The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation.

(4) The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization.

Authority: 21 U.S.C 321, 343, 346, 346a, 348, 350a, 350b, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b-263n.
Source: 45 FR 36390, May 30, 1980, unless otherwise noted.

Database Updated April 1, 2006

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 12, 2006

FROM: Lauren Lee, Pharm.D., Safety Evaluator Team Leader
Division of Drug Risk Evaluation, HFD-430

THROUGH: Rosemary Johann-Liang, M.D., Deputy for
Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430

TO: Bob Rappaport, M.D., Director
Division of Anesthetics, Analgesics, and Rheumatology Products, HFD-170

SUBJECT: OSE Post-Marketing Safety Review (PID#D060611)
Drug: Celebrex (celecoxib); NDA 20-998/S-021
Event: All pediatric adverse events

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

I. EXECUTIVE SUMMARY:

This consult is in response to a request from the Division of Anesthetics, Analgesics, and Rheumatology Products (DAARP) for an AERS review of all pediatric adverse events reported in association with Celebrex (celecoxib) use, in preparation for an upcoming Advisory Committee meeting on November 29, 2006 to discuss the efficacy and safety of celecoxib in the treatment of juvenile rheumatoid arthritis (JRA). Celebrex is currently not approved for use in children.

Celecoxib is a diaryl-substituted pyrazole, a selective inhibitor of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and exhibits anti-inflammatory, analgesic, and antipyretic properties.[1] Celecoxib was first approved in the U.S. on 12/31/1998 for the relief of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) in adults. Following the marketing approval for OA and adult RA, celecoxib was granted approval for ankylosing spondylitis, acute pain in adults, primary dysmenorrhea, and familial adenomatous polyposis (FAP), as an adjunct to usual care. The only COX-2 inhibitor to have been approved for JRA (rofecoxib) was withdrawn from the market in 2004.[2]

[1] Celebrex® (celecoxib) Package Insert, Pfizer, July 2005
[2] An AERS pediatric review of rofecoxib and its use in JRA will be conducted in a separate consult.

The Adverse Event Reporting System (AERS) database was searched for all serious and nonserious pediatric adverse events reported between 12/31/98 and 8/10/06 for celecoxib. The search retrieved 88 cases, of which 31 spontaneous postmarketing reports were included in this case series *(see Section III Table 1. for exclusion criteria).* The age of patients ranged from 4 to 17 years with the mean of 14 years. Of the 30 cases reporting gender, there were 18 females and 12 males. Celecoxib was most commonly used for pain, JRA, and tendonitis. Most of the adverse events were mentioned in only one report, except for rash (4), chest pain (3), hematochezia (2), and headache (2), all of which are labeled events. Notable unlabeled adverse events included pseudoporphyria, epidermolysis bullosa, pericarditis, supraventricular arrhythmia, hypotension, DIC, ARDS, convulsions, and tongue discoloration. Expected adverse events such as acute renal failure, liver failure, leucopenia, neutropenia, thrombopenia, and various skin and GI symptoms were also reported.

Serious outcomes included hospitalization (7), life-threatening (1), and death (1). In the fatal case, a pharmacist called to inquire about whether depression is a side effect of celecoxib because a 15 year old male began taking celecoxib (dose unknown) for pain S/P anterior cruciate ligament reconstruction of the left knee, and he committed suicide 2-3 weeks later. The patient's physician stated that the suspect medication was "Celebrex, claimed by family," but his records did not indicate that he prescribed celecoxib; however, he also stated that it is possible that celecoxib sample was given but not recorded. When he saw the patient last, the patient did not appear to be depressed or suicidal at that time. He had a history of asthma and was concomitantly taking salmeterol, fluticasone, and "various therapeutic products." Both depression and suicide are labeled events for celecoxib. Given the limited information in this case, the relationship between the reported event and celecoxib use was unclear; however, this case was included in the case series because the role of celecoxib could not be excluded.

Most of the adverse events from this case series are included in the labeling for celecoxib; the cases involving unlabeled events are single reports and additional monitoring of adverse events are needed to establish a clear relationship with celecoxib use in the pediatric population. This review contains an analysis of only spontaneous postmarketing pediatric reports, and since celecoxib is currently not approved for use in children, the available information was limited. The sponsor's clinical trial data will likely contain more complete adverse event profile for consideration in determining the overall safety of celecoxib for use in children.

II. BACKGROUND:

DAARP has requested an AERS review of pediatric postmarketing adverse event reports in preparation for an upcoming Advisory Committee meeting on November 29, 2006 to discuss the efficacy and safety of Celebrex (celecoxib) in the treatment of juvenile rheumatoid arthritis (JRA). Celebrex is currently not approved for use in the pediatric population.

Celebrex was approved for marketing in the U.S. on 12/31/98; Celebrex is indicated:

- For relief of the signs and symptoms of osteoarthritis
- For relief of the signs and symptoms of rheumatoid arthritis in adults

- For relief of the signs and symptoms of ankylosing spondylitis
- For the management of acute pain in adults
- For the treatment of primary dysmenorrhea
- To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery)

III. DRUG USE:

See OSE pediatric drug use review by Laura Governale Pharm.D, dated August 30, 2006.[3] According to this review, less than 1% of total dispensed prescriptions for celecoxib were for the pediatric population (0-18 years) from 2002 through June 2006. The majority of prescribing for celecoxib was by general practice and internal medicine specialties. Office-based physician surveys showed that orthopedic surgeons were the most common prescribers of celecoxib for the pediatric population. Sprains and injuries were the most common diagnoses associated with celecoxib.

IV. AERS SEARCH RESULTS:

Between 12/31/98 and 8/10/06, the FDA has received 88 serious and nonserious pediatric (0-17 years) adverse event reports associated with celecoxib in the AERS database. Fifty-seven of 88 cases were excluded from further analyses based on the following:

Table 1. Reasons for exclusion and number of excluded cases

Accidental ingestion	1
Intentional overdose or suicide attempt	3
Duplicate report	3
Adverse event (AE) likely related to another medication	4
AE not clearly identified in the report	4
Maternal exposure[4] • Elective abortion • Drug exposure at 5 months during breastfeeding for 2 days- intestinal obstruction • Drug exposure at 12 months during breastfeeding for 6 months- multiple fractures reported in 3 yr old male • Drug exposure at 4th week of gestation – benign teratoma, cryptorchism	4
Report not involving a pediatric patient or age not provided	5
AE likely related to underlying medical condition or recent surgery	5
Reporter (e.g. MD, French Agency) states that AEs unlikely related to Celebrex or that Celebrex is not a suspect medication	5
AEs from clinical trials [5] *(see Appendix I)*	23
Total	**57**

[3] Governale L, OSE Pediatric Drug Use Review for Celebrex, dated August 30, 2006, available in DFS.
[4] Case reports of celecoxib exposure through the mother (to an infant) was excluded since the sponsor's submission for JRA suggests its use in pediatric patients 2 years and older.
[5] These adverse events reported from clinical trials are not spontaneous postmarketing cases, and therefore, excluded from further review. All of these cases reported the concurrent use of other medications. See Appendix I for a listing of adverse events, demographics, and outcomes of these cases.

V. SUMMARY OF THE CASE SERIES:

Thirty-one cases are included in this case series. A line-listing of the cases are presented in Appendix II.

Individual safety report characteristics (n=31):

Age:	Range (4 – 17 years), Mean (14 years), Median (15 years)
Gender distribution:	Female (18), Male (12), Not reported (1)
Daily dose (n=24):	Range (100-800 mg), Median (200 mg)
Indication for use:	Pain (knee, bone, unspecified etc.—8), JRA (4), tendonitis (2), headache, backache, spondylolisthesis, muscle spasm, knee injury, OA, myalgia, herniated disc, sprained wrist, UTI, menstrual disorder, "ill-defined disorder", malignant neoplasm, and not reported (4)
Onset:	Range (1dose – 6 months), Median (4 days)
Serious outcomes*:	Hospitalization (7), Death (1), Life-threatening (1), Other (10), Not reported (13)
Dec/Rechallenge:	Positive dechallenge (11), Negative dechallenge (1), Positive rechallenge (1)
FDA received date:	1999 (7), 2000 (5), 2001 (7), 2002 (5), 2003 (2), 2004 (2), 2005 (3)
Report type:	Periodic (19), 15 day (10), Direct (2)
Report source:	Physician (13), Pharmacist (4), Nurse (2), Other healthcare professional (3), Consumer/patient (9)
Location:	US (25), Foreign (6)

**more than one possible per report*

The reported adverse events in the cases were categorized according to the AERS system organ classes (SOC) as shown below *(a report may contain more than one adverse event term)*:

- **Blood and lymphatic system disorders**- disseminated intravascular coagulation, leucopenia, neutropenia, thrombopenia
- **Cardiac disorders**- chest pain (3), palpitation, pericarditis, supraventricular arrhythmia
- **Gastrointestinal disorders**- hematochezia (2), abdominal discomfort, vomiting, tongue discoloration, nausea, abdominal pain, constipation
- **General disorders and administration site conditions**- hot flushes, angioneurotic edema, influenza-like illness, weakness, pain, multi-organ failure, lethargy, fatigue
- **Hepatobiliary disorders**- liver function tests abnormal, hepatic failure
- **Infections and infestations**- viral infection, sepsis
- **Investigations**- heart rate decreased, body temperature decreased, electroencephalogram abnormal
- **Musculoskeletal and connective tissue disorders**- bone pain, muscle spasm, swelling of knees
- **Nervous system disorders**- headache (2), dizziness, convulsions, confusion, syncope
- **Renal and urinary disorders**- oliguria, renal impairment, hematuria, urine abnormal, acute renal failure

- **Reproductive system and breast disorders**- menstrual disorder, menstruation irregular
- **Respiratory, thoracic and mediastinal disorders**- laryngotracheal edema, lung infiltration, asthma, bronchospasm, rhinitis, sinusitis, acute respiratory distress syndrome
- **Skin and subcutaneous tissue disorders**- rash (4), skin (toe) ulcer, pruritus, epidermolysis bullosa, pseudoporphyria
- **Surgical and medical procedures**- knee operation
- **Psychiatric disorders**- suicide attempt
- **Vascular disorders**- hypotension

The majority (81%) of the reports were domestic cases. The age of patients ranged from 4 to 17 years with the mean of 14 years. Of the 30 cases reporting gender, there were 18 females and 12 males. Celecoxib was most commonly used for pain, JRA, and tendonitis. No particular pattern was apparent with respect to dose or time of onset of serious adverse events. Most of the above events were mentioned in only one report in this case series, except for rash (4), chest pain (3), hematochezia (2), and headache (2), all of which are labeled events. Notable unlabeled events included porphyria, epidermolysis bullosa, convulsions, pericarditis, supraventricular arrhythmia, hypotension, DIC, ARDS, tongue discoloration, and decreased heart rate. Expected adverse events such as acute renal failure, liver failure, leucopenia, neutropenia, thrombopenia, and various skin and GI symptoms were also reported. Eighteen of 31 cases reported the concomitant use of other medications. Serious outcomes included hospitalization (7), life-threatening (1), and death (1). Positive dechallenge was reported in 11 cases, and positive rechallenge was reported in 1 case. One report of negative dechallenge described a facial rash that did not disappear upon discontinuation of celecoxib and menstrual disorder that was being treated at the time of the report. Both events occurred approximately 17 days after starting celecoxib 200 mg QD for a backache. The patient (15 yo F) was not taking any concomitant medications.

Clinically significant events and notable groupings of selected reactions are discussed in more detail below:

Death

One case of death was identified in this case series, but its association with celecoxib was unclear. A pharmacist called to inquire about whether depression is a side effect of celecoxib because a 15 year old male began taking celecoxib (dose unknown) for pain S/P anterior cruciate ligament reconstruction of the left knee, and he committed suicide 2-3 weeks later. The patient's physician stated that the suspect medication was "Celebrex, claimed by family," but his records did not indicate that he prescribed celecoxib; he also stated that it is possible that celecoxib sample was given but not recorded. When he saw the patient last, the patient did not appear to be depressed or suicidal at that time. He had a history of asthma and was concomitantly taking salmeterol, fluticasone, and "various therapeutic products." Both depression and suicide are labeled events for celecoxib. Given the limited information in this case, the relationship between the reported event and celecoxib use was not clear; however, this case was included in the case series because the role of celecoxib could not be excluded.

Pseudoporphyria

Celecoxib is a benzenesulfonamide derivative, and pseudoporphyria has been reported with sulfonamides as well as NSAIDS. A published case[6] of pseudoporphyria induced by celecoxib described a 12 year old, fair skinned, Caucasian female with JRA who developed "crops of new vesicles and crusted erosions on her face and dorsum of the hands" several weeks after initiating celecoxib. According to the reporting dermatologist, the lesions of pseudoporphyria most closely resembled those of porphyria cutanea tarda clinically and histologically. Within 2 weeks of discontinuing celecoxib therapy, the lesions cleared with residual superficial scarring. This patient had experienced prior outbreaks with similar lesions after treatment with naproxen and nabumetone. In both cases, the lesions cleared after discontinuing NSAID therapy. Although her flares were not always the result of direct sun exposure, her recent lesions with celecoxib did occur toward the end of summer and early fall. This case suggests a causal association between the reported event and the use of celecoxib.

Epidermolysis bullosa

The labeling for celecoxib contains serious skin reactions such as exfoliative dermatitis, Stevens Johnson syndrome (SJS), and toxic epidermal necrolysis. A physician described a case of epidermolysis bullosa involving a 16 year old female who was hospitalized for 7 days after taking celecoxib 200 mg QD for JRA. She was concomitantly taking aspirin. After 24 hours of taking celecoxib, she experienced epidermolysis bullosa, which is a chronic, mostly inherited disease with a rare acquired form; this patient did not have a history of multiple myeloma, amyloidosis, inflammatory bowel disease, and diabetes. There was no significant family history. Celecoxib was discontinued, and the patient was treated with corticosteroids. The event resolved. Given the positive dechallenge and the temporal association, it is possible that the event was associated with celecoxib use.

Blood disorders (leucopenia, neutropenia, thrombopenia)

One foreign case reported leucopenia, neutropenia, and thrombopenia 8 days after starting celecoxib 100 mg BID in a 17 year old male for an ill-defined disorder. Celecoxib was discontinued and the events resolved spontaneously without treatment; laboratory results were not provided. The reporting physician stated that the patient was concomitantly taking valaciclovir at the time of the event, but this drug was not considered a suspect drug since the adverse events resolved before discontinuing valaciclovir. Other concomitant medications included voriconazole and neurontin, but these 2 drugs were also not discontinued at the time when the adverse events were resolved. The patient's medical history was not provided to determine the exact indications for use of these drugs. The above events are labeled for celecoxib, and it is likely that celecoxib was possibly related.

Cardiac disorders (chest pain, pericarditis, premature atrial contractions)

Chest pain was reported in 3 cases, and in all reports, the role of celecoxib could not be excluded. In the first case (15 yo F), chest pain and palpitations were reported after 1 ½ months of celecoxib (200 mg QD) therapy for JRA. Celecoxib was the only drug administered at the time of the event and was subsequently discontinued. The reporting physician did not hear back

[6] Cummins R, Wagner-Weiner L, Paller A. Pseudoporphyria induced by celecoxib in a patient with juvenile rheumatoid arthritis. *J Rheumatology* 1000; 27:2938-2940.

from the patient regarding the outcome. The second case (14 yo M) reported chest pain after 1 week of celecoxib (200 mg QD) therapy for heel pain. Soon after experiencing chest pain, the patient also experienced flu-like symptoms (weakness, "asthma-like symptoms") and possible angioedema. He was seen by a physician and an unspecified testing was done with normal results. Celecoxib was discontinued and the symptoms cleared up. Influenza-like illness, angioedema, and chest pain are all labeled for celecoxib.

There was one case of pericarditis and septic shock involving a 17 year old male, but no other information was available in this foreign case. The report cited celecoxib as the suspect drug so this report was included in this case series, but the cause of the events could not be fully assessed.

Premature atrial contractions were reported in a 17 year old female after 4 days of celecoxib (200 mg BID) therapy for tendonitis. The patient also experienced syncope and confusion. Her medical history included chicken pox the week before taking celecoxib (lesions were scabbing up when celecoxib was started). A CAT scan of the head was negative and seizures were ruled out. An EEG showed increased volume amplitude, indicating that at a resting stage, her brain was not functioning properly. An ECG showed premature atrial contractions. An echocardiogram and 24-hour holter monitor test was normal. The reporter suggested a possible early stage of Reye's syndrome due to celecoxib, but the reported information did not fulfill all the criteria for the diagnosis of Reye's syndrome (e.g. hepatic involvement). Concomitant use of aspirin was not mentioned in the report. Furthermore, according to the report, a direct role of the infectious disease (chicken pox) could not be ruled out. Celecoxib was discontinued, and there was no recurrence of syncope; repeat ECG or EEG were not conducted. The role of celecoxib in association with the reported adverse events could not be excluded in this case.

Hypotension

Celecoxib is labeled for hypertension but not for hypotension. A poorly documented foreign case of hypotension involving a 4 year old male was reported without any background medical history or indication for celecoxib use. In addition to hypotension, he also experienced a decrease in pulse rate, body temperature, and deficient urine volume. Although celecoxib (200 mg BID) was the only suspect drug mentioned in the report, this patient was concomitantly taking many other drugs, including co-trimoxazole, fluconazole, furosemide, lactulose, morphine, and nitrofurantoin (indications unknown). He was treated with fluids and furosemide and recovered. Given the lack of clinical information in this case, a causality assessment could not be made. However, since celecoxib was listed as the primary suspect drug, this case was not excluded.

Gastrointestinal disorders (hematochezia, hematuria, GI upset)

Two cases of hematochezia were reported, and both appeared to be related to the use of celecoxib. Both cases reported that celecoxib was the only drug taken for herniated disc and tendonitis, respectively. The onset was 15 days (17 yo M) and 2 days (17 yo F), respectively. The administered dose was 200 mg QD in both cases. Medical history included no prior rectal bleeding in one case, and mitral valve prolapse in the second case. This event is labeled for celecoxib.

Hematuria, which is also labeled, was reported in one case involving a 13 year old male with spondylolisthesis, who had taken celecoxib 200 mg QD. Approximately 6 months after starting celecoxib, blood and mucous was found in his urine. The patient's physician expressed concerns about continuing celecoxib therapy. Concomitant medication included cetirizine. His medical history included viral myocarditis and urinary frequency (past 3 years); he also has a pacemaker. It is possible that celecoxib contributed to the reported event.

"Toe ulcer and GI upset" were reported in a 13 year old male who had taken celecoxib 100 mg BID for bone pain. Time of onset was not reported. Concomitant medications included amitriptylline, ranitidine, morphine, acetaminophen, and mupirocin; however, none of these medications were listed as a suspect drug, except for celecoxib. Past medical history included osteosarcoma and Raynaud's syndrome. This case contains many confounders, but the contributory role of celecoxib could not be excluded.

Viral infection

Viral infection is a labeled event for celecoxib. In one case, a 4 year old male with metastatic epithelioid hemangioendothelioma to the lung, liver, bone, and brain, was treated with celecoxib, Cytoxan, etoposide, and thalidomide. Shortly after initiation of celecoxib, the child began to experience a decrease in lung function and abdominal pain. A month later, celecoxib dose was increased from 100 mg QD to 200 mg BID after reviewing a CT scan which revealed an increase in the size of the tumors in the liver. Few weeks later, the child was hospitalized due to a viral infection; a bronchoscopy revealed airway edema, but no tumors. Additional information was not available. In this case, it is likely that the patient's underlying disease and chemotherapy are responsible for the lower resistance to infections. However, this report was included in the case series since celecoxib is labeled for viral infection, and it is possible that celecoxib could have contributed to the adverse event.

Renal disorders (acute renal failure, renal dysfunction)

Two cases reported renal adverse events, but lacked clinical details in the reports. The first case involved a 14 year old female who experienced renal failure after approximately 4 months of celecoxib therapy (100 mg BID) for pain. The patient was not taking any other medication. Additional information was not provided, except that the patient had foot surgery 5 days prior to the reported event date. Celecoxib was listed as the suspect drug by the physician. The second case involved a 12 year old (sex unknown) who experienced renal dysfunction, elevated liver enzymes, and rash after taking celecoxib 200 mg for 3 days (indication unknown). The reporting physician stated that it may be "Celebrex toxicity", but no further information was available on this case. The events described above are all labeled for celecoxib so it is possible that these events were associated with its use. The second case in particular suggests an allergic component as well. However, additional clinical details are needed to establish a causal relationship.

Liver failure

One case reported liver failure, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and multi-organ failure with celecoxib and levofloxacin use. A 17 year old female with no prior significant history or medication use was diagnosed with UTI and prescribed levofloxacin 500 mg QD and celecoxib 200 mg QD. The patient failed to improve and presented 4 days later with increased abdominal pain, mildly increased liver enzymes (AST

~ 80), and persistent UTI, leading to hospitalization. Levofloxacin po was switched to IV, but the patient continued to decline over the next 72 hours (AST~ 300). It was considered that her hepatopathy was related to levofloxacin, which is labeled for liver failure. The report did not specify when celecoxib was discontinued. Cetriaxone and acetaminophen/hydrocodone (for pain/fever) were started. She underwent a HIDA scan, abdominal CT scan, and an ultrasound, which revealed minimal ascites, otherwise non-diagnostic findings. Due to the progressively increasing LFTs (lab results not provided), hypotension, and fever, the patient underwent an exploratory laparotomy, which was unremarkable with the exception of diffuse mesenteric adenopathy. Her organs appeared normal. Post-operatively, she required vasopressor therapy for hypotension and mechanical ventilation for ARDS. She developed DIC and multi-organ failure. Blood cultures were negative and multiple diagnostic studies were performed with non-diagnostic findings. She was started on IV steroids with continued antibiotic therapy and supportive care. She responded to treatment and improved. Her physician stated that she was doing well after discharge and considered the events to be possibly related to levofloxacin with celecoxib as a co-suspect medication.

Convulsions

Celecoxib is not labeled for convulsions. A physician reported that a 16 year old male with muscular pain (due to chronic compartment syndrome), who was treated with celecoxib (dose unknown), experienced convulsions after 2 days of treatment. He was admitted to a hospital where he remained for 24 hours. Toxicological examination, CT scan, and MRI findings were all normal. At the time of the report, the patient was receiving prophylactic treatment with valproate without any further events. This patient was also taking clarithromycin at the time of the event, which is labeled for seizures. Two weeks after the event, the patient's compartment syndrome was successfully treated with fasciotomy. Given the available clinical information in this case, the role of celecoxib could not be clearly established.

VI. CONCLUSION:

The Adverse Event Reporting System (AERS) database was searched for all serious and nonserious pediatric adverse events reported between 12/31/98 and 8/10/06 for celecoxib. Thirty-one spontaneous postmarketing reports were included in this case series. The age of patients ranged from 4 to 17 years with the mean of 14 years. Of the 30 cases reporting gender, there were 18 females and 12 males. Celecoxib was most commonly used for pain, JRA, and tendonitis. Most of the adverse events were mentioned in only one report, except for rash (4), chest pain (3), hematochezia (2), and headache (2), all of which are labeled events. Notable unlabeled adverse events included pseudoporphyria, epidermolysis bullosa, pericarditis, supraventricular arrhythmia, hypotension, DIC, ARDS, convulsions, and tongue discoloration. Expected adverse events such as acute renal failure, liver failure, leucopenia, neutropenia, thrombopenia, and various skin and GI symptoms were also reported.

Serious outcomes included hospitalization (7), life-threatening (1), and death (1). In the fatal case, a pharmacist called to inquire about whether depression is a side effect of celecoxib because a 15 year old male began taking celecoxib (dose unknown) for pain S/P anterior cruciate ligament reconstruction of the left knee, and he committed suicide 2-3 weeks later. The patient's physician stated that the suspect medication was "Celebrex, claimed by family," but his records

did not indicate that he prescribed celecoxib; however, he also stated that it is possible that celecoxib sample was given but not recorded. When he saw the patient last, the patient did not appear to be depressed or suicidal at that time. He had a history of asthma and was concomitantly taking salmeterol, fluticasone, and "various therapeutic products." Both depression and suicide are labeled events for celecoxib. Given the limited information in this case, the relationship between the reported event and celecoxib use was unclear; however, this case was included in the case series because the role of celecoxib could not be excluded.

Most of the adverse events from this case series are included in the labeling for celecoxib; the cases involving unlabeled events are single reports and additional monitoring of adverse events are needed to establish a clear relationship with celecoxib use in the pediatric population. This review contains an analysis of only spontaneous postmarketing pediatric reports, and since celecoxib is currently not approved for use in children, the available information was limited. The sponsor's clinical trial data will likely contain more complete adverse event profile for consideration in determining the overall safety of celecoxib for use in children.

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Lauren Y. Lee, Pharm.D.
Safety Evaluator Team Leader

APPENDIX I

Adverse events reported from clinical trials:

- **A non-IND clinical study (Dana Farber Cancer Institute Protocol)- anti-angiogenic chemotherapy: a phase II trial of thalidomide, celecoxib, etoposide, and cyclophosphamide in patients with relapsed or progressive cancer**

ISR#	Age	Sex	Year*	Outcome**	Reported Event
3850754-8	11 mos	F	2001	HO	Tachypnoea, URI, wheezing, vomiting
4221666-5	1Y	F	2002	HO, LT	Delayed gastric emptying, vomiting, lethargy, irritability, status epilepticus
3769968-0	32 mos	M	2001	DE, HO	Disease progression, hemiparesis, ataxia, vomiting
3909653-5	3Y	M	2002	HO	Gastroenteritis, cryptosporidial infection, anorexia, constipation, diarrhea, irritability, vomiting
4006598-X	3Y	M	2002	Other	Neutropenia
4098383-8	4Y	M	2003	HO	Hypokalemia, pneumatosis, diarrhea, vomiting, neutropenia, leucopenia
4227269-0	5Y	M	2002	HO	Ventriculoperitoneal shunt malfunction, neutropenia, leucopenia
3896932-3	6Y	M	2002	DE	Death disease progression, dysphagia
4007324-0	6Y	M	2001	HO	Convulsion, dehydration, infection, nausea, vomiting
3850755-X	8Y	F	2001	DE	Death, disease progression
4221482-4	8Y	F	2003	HO, RI	Disease progression, delusions, hallucinations, confusion, abnormal behavior, anxiety, stress
4485832-6	8Y	M	2003	HO	Cellulitis, wart, neutropenia, leucopenia, syncope, hemoglobin decreased
4007329-x	10Y	M	2002	HO	Neutropenia, infection, cough aggravated dyspnea, nausea, pyrexia
3891102-7	13Y	F	2002	DE, HO	Death, loss of consciousness, respiratory distress, disease progression, pain, restlessness
3908986-6	15Y	F	2001	HO	Disease progression, cellulitis, hematocrit decreased, ovarian failure, speech disorder, amenorrhea, constipation, depression, fatigue, gait abnormal, headache, peripheral neuropathy, RBC decreased, vomiting, WBC decreased
4006494-8	15Y	M	2002	HO	Foot ulcer, peripheral neuropathy
4006599-1	15Y	M	2002	Other	Febrile neutropenia, neutropenia, sore throat
4006655-8	15Y	M	2001	HO	Constipation, abdominal pain, neutropenia, pyrexia, blood in stool, urinary retention, ataxia, diarrhea, dysphasia, fatigue, hypothyroidism, edema, pain, peripheral neuropathy
4953846-5	15Y	M	2006	LT	Agranulocytosis
4006511-5	16Y	M	2002	HO	Deep venous thrombosis

- **A randomized, double-blind, multicenter, active-controlled parallel-group study to evaluate the efficacy and safety of celecoxib suspension compared to naproxen in patients with JRA**

ISR#	Age	Sex	Year*	Outcome**	Reported Event
4544654-8	8Y	F	2004	HO	Acute CMV hepatitis (concomitantly with methotrexate, Tylenol)

- **An open-label, multicenter pilot study to evaluate the efficacy and safety of low-dose chemotherapy (vinblastine) and COX-II inhibitor (celecoxib) as anti-angiogenic therapy in children with progressive or recurrent solid tumors**

ISR#	Age	Sex	Year*	Outcome**	Reported Event
4077641-7	16Y	F	2003	HO	Febrile neutropenia

• **An investigative therapy protocol (635-ONC-0509-001) using Vinblastine and Celebrex**					
ISR#	Age	Sex	Year*	Outcome**	Reported Event
4493033-0	8Y	M	2003	DE, HO	End stage renal cell carcinoma, congestive heart failure, rectal hemorrhage, anemia, tachycardia, mitochondrial myopathy

*Year of the reported event

**HO= hospitalization; DE= death; LT=life-threatening; RI= required intervention

APPENDIX II

Line listing of celecoxib case series (N=31):

ISR#	Age (yrs)	Sex	Daily Dose (mg)	Indication	Outcome	FDA Receipt Year	Event
3717457-1	4	M	100 QD	Malignant neoplasm	HO	2001	Viral infection, laryngotracheal edema
3947081-7	4	M	200 BID	--	Other	2002	Hypotension, heart rate decreased, body temperature decreased, oliguria
3353171-2	11	M	100 QD	HA	--	1999	Hot flushes, headache
4308576-x	12	---	200 ---	---	HO	2004	Renal impairment, LFT abnormal, rash
3653056-8	12	F	--	JRA	--	2001	Pseudoporphyria
3651696-3	13	M	200 QD	Spondylolisthesis	--	2001	Hematuria, urine abnormal
3945881-0	13	M	100 BID	Bone pain	Other	2002	Bone pain, toe ulcer, GI upset
4175799-2	13	F	100-200 QD	--	Other	2003	Lung infiltration
3528719-5	14	F	--	RA	---	2000	Chest pain, pruritus
3911407-0	14	M	200 QD	Pain	Other	2002	Chest pain, angioneurotic edema, influenza-like illness, weakness, asthma
3528491-9	14	F	200 QD	Pain	--	2000	Wheezing (bronchospasm), rhinitis
3378516-9	14	F	100 QD	Muscle spasm	---	1999	Vomiting
3531102-x	14	F	100 BID	Pain	HO	2000	Acute renal failure
3242233-6	15	F	---	Knee joint pain	Other	1999	Muscle cramping
3584808-0	15	M	200 QD	JRA	---	2000	Chest pain, palpitation
3723163-x	15	F	---	Knee injury	---	2001	Tongue discoloration
3821122-x	15	F	100 BID	OA	---	2001	Sinusitis
3645457-9	15	M	---	knee pain post surgery	Death	2001	Suicide attempt
3350086-0	15	F	100 BID	Pain	---	1999	Dizziness, nausea, headache
3528855-3	15	F	200 QD	Backache	--	2000	Rash, irregular menstrual period
3662215-x	16	F	200 QD	JRA	HO	2001	Epidermolysis bullosa
4074826-0	16	M	---	Myalgia	HO	2003	Convulsion
3308680-9	17	M	200 QD	Herniated disc	Other	1999	Hematochezia, abdominal pain
3323703-9	17	F	100 BID	Sprained wrist	---	1999	Rash, pain
4332919-4	17	F	200 QD	UTI	LT, HO	2004	Multi-organ failure, ARDS, hepatic failure, DIC
3379782-6	17	F	100 QD	Menstrual disorder	---	1999	Constipation
3947723-6	17	M	---	----	HO	2002	Septic shock, pericarditis
4699256-X	17	M	100 BID	Ill-defined disorder	Other	2005	Leucopenia, neutropenia, thrombopenia
4723139-x	17	F	200 QD	Tendonitis	Other	2005	Haematochezia
3921358-3	17	F	400 BID	Tendonitis	Other	2002	Lethargy, fatigue, confusion, syncope, supraventricular arrhythmia, electroencephalogram abnormal
4701079-x	17	F	200 BID	Knee pain	Other	2005	Menstrual irregularity, rash, swelling of knee

**Reported outcomes: DE=death, HO=hospitalized, LT=life threatening

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/s/

Lauren Lee
10/16/2006 09:07:42 AM
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang
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