FDA Background Package for the Arthritis Advisory Committee Meeting, April 12, 2007

- **New Drug Applications (NDA) #--**21-389 and 21-772
- **Product Name--**Arcoxia (etoricoxib) tablets, 30 and 60 mg
- **Applicant--**Merck & Co., Inc.
- **Indication—**For the relief of the signs and symptoms of osteoarthritis
- **Review Division--**Division of Anesthesia, Analgesia and Rheumatology Products (DAARP), Bob A. Rappaport, M.D., Director

GUIDE TO FDA BACKGROUND PACKAGE
APRIL 12, 2007 ARTHRITIS ADVISORY COMMITTEE (AAC) MEETING

This background package consists of the below-listed documents in the following order

Document #	General topic	Description	Reason included
1	Introduction	Dr. Rappaport's Memo to Advisory Committee Members	Introduction to purpose of meeting and issues to be considered.
2	February 2005 AAC Meeting	Flash minutes from February 2005 Arthritis Advisory Committee Meeting	Brief description of issues discussed and voting on Agency questions from February 2005 AC Meeting.
3	February 2005 AAC Meeting	AAC Meeting transcript-2/17/05	Merck presentation--pages 152-188 FDA presentation--pages 188-201 Panel Discussion--pages 347-387
4	Agency position on NSAIDs	FDA Decisional Memo, Drs. Jenkins and Seligman	Articulates Agency's thinking regarding NSAIDs/COX-2 inhibitors in 2005
5	Agency position on NSAIDs	NSAID Package Insert template	Includes language required by FDA for NSAIDs following Decisional Memo
6	Agency position on NSAIDs	NSAID Medication Guide template	Includes language required by FDA for NSAIDs following Decisional Memo
7	FDA review of current submission	Expanded Executive Summary from Medical Officer's review	Articulates Agency review of efficacy and safety data relevant to current submission
8	FDA review of current submission	Executive Summary from Statistician's review	Describes Agency review of safety data
9	General	Bibliography of referenced articles	Provides references for articles cited
10-14	General	Citations for selected references	• Three journal articles regarding NSAIDs and GI toxicity including one description of the MEDAL data. • Two editorials regarding the MEDAL Program.

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: March 21, 2007

FROM: Bob A. Rappaport, MD
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

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

RE: Overview of the April 12, 2007 AAC Meeting to Discuss NDA 21-772 for Arcoxia for the treatment of Rheumatoid Arthritis

As I noted in my memo for the last meeting of this committee (Celebrex for Juvenile Rheumatoid Arthritis), one of the results of the withdrawal of Vioxx from the market due to safety concerns in September of 2004 is an increased level of scrutiny of the cardiovascular safety of the COX-2 selective and, indeed, of all NSAID drug products. This increased scrutiny comes from all quarters, the Agency, the pharmaceutical industry, academia, the press, various advocacy groups and Congress. As part of examining the safety of the NSAIDs overall and the COX-2 drugs specifically, numerous analyses of the available controlled and observational data regarding the potential cardiovascular toxicity of these products 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 exposed to NSAIDs, the exact degree of this risk and the underlying pathophysiology for these events remain controversial.

Nevertheless, after a thorough consideration of the available data and published analyses, the Agency has provided a clear position regarding the potential approval of new NSAIDs, and in particular COX-2 selective NSAIDs, in the form of a memo signed on April 6, 2005 by Dr. John Jenkins, Director of the Office of New Drugs, and Dr. Paul Seligman, who at the time was Director of the Office of Pharmacoepidemiology and Statistical Science. In that memo, Drs. Jenkins and Seligman concluded the following:

- The three approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib, and valdecoxib) are associated with an increased risk of serious adverse CV events compared to placebo. The available data do not permit a rank ordering of these drugs with regard to CV risk.

- Data from large long-term controlled clinical trials that have included a comparison of COX-2 selective and non-selective NSAIDs do not clearly demonstrate that the COX-2 selective agents confer a greater risk of serious adverse CV events than non-selective NSAIDs.

- Long-term placebo-controlled clinical trial data are not available to adequately assess the potential for the non-selective NSAIDs to increase the risk of serious adverse CV events.

- Pending the availability of additional long-term controlled clinical trial data, the available data are best interpreted as being consistent with a class effect of an increased risk of serious adverse CV events for COX-2 selective and non-selective NSAIDs.

- 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 is 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).

Based on these conclusions, the Agency now focuses its evaluations of applications for new NSAID drug products specifically on the risks for cardiovascular toxicity, in addition to the other commonly known safety issues for this class (e.g., gastrointestinal, and renal adverse effects). A new product that appears to have an increased overall risk profile for CV disease, particularly beyond that seen with other drugs in the class, would not be appropriate for marketing approval unless the product fills an unmet need for a particular patient population that has no relatively safer approved products available to them, and provides a reasonable risk to benefit balance for that patient population.

Merck submitted their application for Arcoxia on October 24, 2006, for the indication of relief of the signs and symptoms of osteoarthritis. Arcoxia is a COX-2 selective NSAID that has been approved in many countries in Europe, South America, and Asia, with the first approval occurring in 2001. Merck has submitted data in support of their position that Arcoxia results in less gastrointestinal toxicity than the currently approved non-selective NSAIDs for the proposed patient population, and that it is no less safe than approved NSAID drug products and has no novel toxicities that would prevent its inclusion in the approved NSAID armamentarium.

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

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

- the results of the clinical studies performed in support of the application for Arcoxia; and

- analyses performed to assess the efficacy, safety and risk to benefit ratio of this new drug product.

Following these presentations, you will be asked to assess these findings, to discuss the apparent risks and benefits of Arcoxia, and, finally, to vote on whether the AAC should recommend to the Agency that Arcoxia be approved as an additional treatment for the relief of the signs and symptoms of osteoarthritis.

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. Obviously, given the medical and regulatory experience of recent years regarding the risk profile of NSAIDs, the approval of a new COX-2 selective NSAID product must be undertaken with due care and caution. Thank you in advance for your advice, which will aid us in making the most informed and appropriate decision possible.

February 2005 Arthritis Advisory Committee Meeting Flash Minutes

(16 pages)

These summary minutes for the February 16, 17 and 18, 2005, Joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee were approved on ___3/7/05____.

I certify that I attended the February 16, 17 and 18, 2005, Joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____//S//_____ _____//S//_____
LCDR Dornette Spell-LeSane, MHA, NP-C Alastair Wood, M.D.
Supervisory Health Science Administrator Chair

For, Kimberly Topper, M.S., Executive Secretary

Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee
February 16, 17, and 18, 2005

The following is an internal report, which has not been reviewed. It is not meant to be a comprehensive review of the meeting. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder05.html#ArthritisDrugs. Slides shown at the meeting will be available at the same website.

All external requests for the meeting minutes and transcripts should be submitted to the CDER Freedom of Information office.

Joint Meeting of The Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on February 16, 17 &18, 2005, at the Hilton, located at 620 Perry Parkway, Gaithersburg, Maryland to discuss the overall benefit to risk considerations (including cardiovascular and gastrointestinal safety concerns) for COX-2 selective nonsteroidal anti-inflammatory drugs and related agents. The meeting was chaired by Alastair J.J. Wood, M.D.

Arthritis Advisory Committee Members Present (voting):
Joan Bathon, M.D., Dennis Boulware, M.D., John J. Cush, M.D., Michael Finley, D.O., Allan Gibofsky, M.D., Gary Hoffman, M.D., Norman Ilowite, M.D., Susan Manzi, M. M.D., M.P.H.

Drug Safety and Risk Management Advisory Committee Members Present (voting):
Stephanie Y. Crawford, Ph.D., Ruth S. Day, Ph.D., Curt D. Furberg, M.D., Ph.D., Jacqueline S.Gardner, Ph.D., MPH, Peter A. Gross, M.D., Eric S. Holmboe, M.D. Arthur A. Levin, M.P.H., Louis A. Morris, Ph.D., Richard Platt, M.D., M.Sc, Robyn S. Shapiro, J.D., Annette Stemhagen, Dr.Ph

SGE Consultants (voting):
Alastair J.J. Wood, M.D., Steve Abramson, M.D., Steven L. Shafer, M.D., Robert H. Dworkin, Ph.D., Steven Nissen, M.D., Charles H. Hennekens, M.D., Emile Paganini, M.D., Leona Malone, L.C.S.W., (Patient Rep) **,** Thomas Fleming, Ph.D., John T. Farrar,M.D., Janet Elashoff, Ph.D., Ralph D'Agostino, Ph.D.

SGE Consultants (non voting):
Cryer, Byron, M.D., (Speaker and Discussant) Packer, Milton M.D., (Speaker only)

National Institute of Health Participants (voting):
Richard O. Cannon III, M.D., Michael J. Domanski, M.D., Lawrence Friedman, M.D.

FDA Invited Guest Speakers (non-voting):
Garret A. FitzGerald, M.D., Ernest Hawk, M.D., M.P.H., Constantine Lyketsos, M.D., M.H.S., Bernard Levin, M.D.

FDA Participants at the Table:
Jonca Bull, M.D., Brian Harvey, M.D., John Jenkins, M.D., Sandra Kweder, M.D., Robert O'Neil, Ph.D., Paul Seligman, M.D., Steve Galson, M.D., Robert Temple, M.D., Anne Trontell, M.D., M.P.H.

FDA Presentors:
David Graham, M.D., M.P.H., Sharon Hertz, M.D., Joel Schiffenbauer, M.D., Lourdes Villalba, M.D., James Witter, M.D.

Open Public Hearing Speakers:

Joan Brierton Johnson and Sabrina	
Sidney M. Wolfe, MD	Director, Public Citizen's Health Research Group
Linda Suydam	Vice President, Regulatory and Scientific Affairs, Consumer Healthcare Products Association - CHPA
Jennifer Lo, Ph.D. and	CEO & President, BioJENC, LLC, Louisiana Business & Technology Center
Gene Luther, D.V.M., Ph.D.	
Jim Tozzi	Member, Board of Advisors, Center for Regulatory Effectiveness
Diana Zuckerman, Ph.D.	President, National Research Center for Women & Families
Elizabeth Tindall, MD	President, American College of Rheumatology
Dimitra Poulos	
John Pippin, M.D.	Physicians Coomittee for Responsible Medicine
MAJ Christopher Grubb, M.D.	Womack Army Medical Center, Department of Anesthesiology and Pain Management
Janet Arrowsmith-Lowe, MD	President, Arrowsmith-Lowe Consulting, Inc.
Mark H. Einstein, M.D.	Assistant Professor, Division of Gynecologic Oncology, Department of Obstetrics & Gynecology and Women's Health Montefiore Medical Center
John Abramson M.D.	Harvard Medical School
Herbert S. B. Baraf, MD, FACP, FACR	Clinical Professor of Medicine, George Washington University
Max Hamburger MD	
Waqar Qureshi, MD, FACP, FACG	Associate Professor of Medicine, Chief of Endoscopy, Baylor College of Medicine
David P. Matthews	
W. Hayes Wilson, MD	Chief of Rheumatology, Piedmont Hospital President, Piedmont Rheumatology Consultants, PC
Gary W. Williams, M.D., Ph.D.	Chairman, Department of Medicine and Vice President of Medicine Services, at Scripps Clinic and Research Foundation
Rebecca Burkholder	Director of Health Policy, National Consumers League
Amye L. Leong, MBA	President & CEO, Healthy Motivation, Spokesperson, UN-endorsed Bone and Joint decade 2000-2010

Donna Marie Fox- Keidel	
Theresa Ray	
Judith Whitmire	
Judy Fogel	Brigham & Women's Hospital, Harvard Medical School
R. Preston Mason, Ph.D.	Brigham & Women's Hospital, Harvard Medical School
Gurkirpal Singh, MD	Adjunct Clinical Professor of Medicine Division of Gastroenterology and Hepatology Stanford University School of Medicine
Dr. Allan N. Fields	
Grant Johnson	
Necole Kelly	President, American Chronic Pain Association
Robert Thibadeau, Ph.D.	
Lawrence Goldkind MD	Assistant Professor of Medicine, Department of Gastroenterology, Uniformed Services University of Health Sciences
Susan Winckler, RPh, Esq.,	APhA's Vice President of Policy and Communications and Staff Counsel
Virginia Ladd	President American Autoimmune Related Diseases Association (AARDA)
Paola Patrignani, Ph.D.	Professor of Pharmacology, Department of Medicine and Center of Excellence on Aging, "G. d'Annunzio" University
Betsy Chaney	
Dr. John Klippel	President and CEO of the Arthritis Foundation
Carol Spitz	
Eileen Lacijan	
Gloria Barthelmes	
Rebecca Dachman	
Michael D. Paranzino	President, *Psoriasis Cure Now!*
Dr. Glenn Eisen	Oregon Health Sciences University
Yvonne Sherrer, M.D.	

The members and the invited consultants were provided with the background material from the FDA, Merck, Pfizer, Novartis, Hoffmann-La Roche Inc., and Bayer Healthcare LLC, Consumer Care Division prior to the meeting.

The meeting was called to order at 8:00 a.m. each day by Alastair Wood, M.D. The Committee members, consultants, and FDA participants introduced themselves. The conflict of interest statement was read into the record each day by the Executive Secretary, Kimberly Littleton Topper, M.S. There were approximately 600 people in attendance. The agenda proceeded as follows:

Wednesday, February 16, 2005

Call to Order Conflict of Interest Statement	Alastair J. J. Wood, M.D., Chair Kimberly Littleton Topper, M.S. Executive Secretary
Welcome	Steven Galson, M.D., M.P.H. Acting Director, Center for Drug Evaluation and Research (CDER)
Regulatory History	Jonca Bull, M.D. Director, Office of Drug Evaluation V, CDER
Gastrointestinal Effects of NSAIDs and COX-2 Specific Inhibitors	Byron Cryer, M.D. University of Texas Southwestern Medical School
Mechanism Based Adverse Cardiovascular Events and Specific Inhibitors of COX-2	Garret A. FitzGerald, M.D. University of Pennsylvania School of Medicine
Committee Questions to Speakers	
Break	
Vioxx (rofecoxib) ***Sponsor Presentation:***	
Rofecoxib	Ned S. Braunstein, M.D. Senior Director Merck Research Laboratories
FDA Presentation:	
Vioxx Cardiovascular Safety	Lourdes Villalba, M.D. Medical Officer, CDER
Committee Questions to Speakers	
Lunch	

Celebrex (celecoxib)

Sponsor Presentation:

Introduction	Joseph M. Feczko, M.D. Senior Vice President, Pfizer Global Research and Development, and President, Worldwide Development

Wednesday, February 16, 2005 (cont.)

Cardiovascular Safety and Risk/Benefit Assessment of Celecoxib	Kenneth M. Verburg, Ph.D. Vice President, Inflammation and Immunology, Clinical Research and Development, Pfizer Global Research and Development

FDA Presentation:

COX-2 CV Safety: celecoxib	James Witter, M.D., Ph.D. Lead Medical Officer, CDER

NIH and Investigator Presentation:

Celecoxib in Adenoma Prevention Trials: The APC Trial (Prevention of Sporadic Colorectal Adenomas with Celecoxib)	Ernest Hawk, M.D., MPH Director, Office of Centers, Training, & Resources NCI/OD/NIH
The PreSAP Trial (Prevention of Colorectal Sporadic Adenomatous Polyps)	Bernard Levin, M.D M.D. Anderson Cancer Center The University of Texas

Committee Questions to Speakers

Break

Bextra (valdecoxib) and parecoxib

Sponsor Presentation:

Cardiovascular Safety and Risk/Benefit Assessment of Valdecoxib and Parecoxib	Kenneth M. Verburg, Ph.D.
Closing	Joseph M. Feczko, M.D.

FDA Presentation:

COX-2 CV Safety: valdecoxib – parecoxib	James Witter, M.D., Ph.D.

Naproxen

Sponsor Presentation:

Bayer and Roche Joint Presentation on Naproxen	Leonard M. Baum, R.Ph. Vice President, Regulatory Affairs Bayer HealthCare Consumer Care Division Martin H. Huber, M.D. Vice President, Global Head Drug Safety Risk Management, Hoffmann-La Roche, Inc.

Committee Questions to Speakers

Thursday, February 17, 2005

Call to Order Conflict of Interest Statement	Alastair J. J. Wood, M.D., Chair Kimberly Littleton Topper, M.S.
Interpretation of Observational Studies of Cardiovascular Risk of Non-steroidal Drugs	Richard Platt, M.D., M.S. Harvard Medical School
Review of Epidemiologic Studies on Cardiovascular Risk with Selected NSAIDs	David Graham, M.D., M.P.H. Medical Officer, CDER
Committee Questions to Speakers	
Arcoxia (etoricoxib) ***Sponsor Presentation:*** Etoricoxib	Sean P. Curtis, M.D. Senior Director, Clinical Research Merck Research Laboratories
FDA Presentation: Analysis of Cardiovascular Thromboembolic Events With Etoricoxib	Joel Schiffenbauer, M.D. Medical Officer, CDER
	Break
Lumiracoxib ***Sponsor Presentation:*** Lumiracoxib: Introduction	Mathias Hukkelhoven, Ph.D. Senior Vice President and Global Head, Drug Regulatory Affairs Novartis Pharmaceuticals Corporation
Gastrointestinal and Cardiovascular Safety of Lumiracoxib, Ibuprofen, and Naproxen	Patrice Matchaba, M.D. Global Medical Director Lumiracoxib Program, Novartis Pharmaceuticals Corporation
FDA Presentation: Lumiracoxib	Lourdes Villalba, M.D. Medical Officer, CDER
Committee Questions to Speakers	
Lunch	
Open Public Hearing	
Break	
Committee Discussion	

Friday, February 18, 2005

Call to Order	Alastair J. J. Wood, M.D.,Chair
Conflict of Interest Statement	Kimberly Littleton Topper, M.S.

Naproxen
Investigator Presentation:

Alzheimer's Prevention Study: ADAPT (Alzheimer's Disease Anti-Inflammatory Prevention Trial)	Constantine Lyketsos, M.D. The John Hopkins Hospital

Additional Background Presentations

Interpretation of Observed Differences in the Frequency of Events When the Number of Events is Small	Milton Packer, M.D. University of Texas Southwestern Medical School
Committee Questions to Speakers	
Clinical Trial Design and Patient Safety: Future Directions for COX-2 selective NSAIDs	Robert Temple, M.D. Director, Office of Medical Policy, CDER
Issues in Projecting Increased Risk of Cardiovascular Events to the Exposed Population	Robert O'Neill, Ph.D. Director, Office of Biostatistics, CDER
Committee Questions to Speakers	
Break	
Risk Management Options for Action ***(added to agenda on 2/18/05)***	Anne Trontell, M.D., M.P.H. Deputy Director, Office of Drug Safety
Summary of Meeting Presentations	Sharon Hertz, M.D. Deputy Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products, CDER
Advisory Committee Discussion of Questions	
Lunch	
Advisory Committee Discussion of Questions	
Break	
Advisory Committee Discussion of Questions	
Meeting Wrap-up	Alastair J. J. Wood, M.D.
Adjourn	

Thursday, February 17, 2005:

Discussion Points:

1. Please discuss the available data regarding the potential cardiovascular (CV) risk for the non-selective and COX-2 selective NSAIDs. Please discuss whether the available data support a conclusion that increased CV risk is a class effect for all NSAIDs, the COX-2 selective NSAIDs only, or only for certain agents within the class. Also, please discuss the possible mechanism(s) of action for an increased cardiovascular risk with these agents.

The Committee shared various opinions with the members agreeing, in general, that there was inadequate data to draw a definite conclusion regarding whether a class effect exists. However, that being said, they agreed that it did appear likely that for at least the three approved COX-2 products, a class effect appears to be present. They further indicated that they believed that if sufficient drug was given in high enough doses to high risk patients an increase incidence of cardiovascular events would be yielded. There is a dearth of data on the other NSAIDs and the consensus of the Committee was that each drug should be individually evaluated for CV risk. It is unknown whether a CV signal is present across all the products, with possible different mechanisms of action, but each is suspect when used chronically and until proven otherwise, patients/physicians should be warned.

2. Please discuss the contributions and limitations of the currently available observational studies to the assessment of CV risk for the non-selective and COX-2 selective NSAIDs. In particular, please discuss the role of such observational studies in informing regulatory decisions about post-marketing safety issues.

While the Committee stated various opinions, most agreed that observational studies do provide useful, although limited, information. In general, observational studies are supplementary to randomized, controlled, clinical trials (RCT) since selection bias is likely present. Additional comments provided by the committee were:

- **Observational studies are supplementary to Randomized Control Trials (RCT)**
- **With COX-2 products, there is good correlation between observational and RCT trials**
- **Long term follow up after drop out from RCT is necessary**
- **More observational studies on older drugs are needed**
- **FDA review of observational studies does not follow the same process standards used by FDA in reviewing RCTs**
- **Observational studies are most helpful if they find a strong and consistent association across studies, with a hazard ratio greater than 2 or 3; Observational studies with hazard ratios under 2, even if statistically significant, are difficult to interpret since low but precise estimates of risk may be due to residual confounding or biases**
- **Observational studies can be classified as "hypothesis generating"; they provide clues as to whether and if to conduct RCTs but observational studies do not establish casuality**

3. Please discuss the available data regarding the potential benefits of COX-2 selective NSAIDs versus non-selective NSAIDs and how any such benefits should be weighed in assessing the potential benefits versus the potential risks of COX-2 selective agents from a regulatory perspective.

Overall the committee felt that the GI benefits should not be minimized, however, the GI benefits of the COX-2s appear to be less than first reported. Vioxx is the only product with GI benefit in labeling; no clear data that show GI benefit for Celebrex and Bextra. Although not a benign event, a GI event is in most cases not as permanently disabling as a myocardial infarction or a stroke. The Committee members offered the following additional considerations for weighing benefit versus risk:

- ***Benefit versus risk in patients who do not tolerate nonselective NSAIDs should be considered***
- ***Pain relief should be considered***
- ***If no clear benefit, there should be an extremely low threshold for increased CV risk***
- ***Pediatric issues should be considered; there are fewer choices in this population and only 3 NSAIDs are approved for use in pediatric population, only 2 liquid formulations***
- ***Tolerability - fewer serious GI events, but a lot of symptoms should be considered***

Friday, February 18, 2005

Questions to the Committee

Approved products

Three COX-2 selective NSAIDs are currently approved for marketing in the United States; celecoxib (Celebrex), rofecoxib (Vioxx) and valdecoxib (Bextra). The original approvals and subsequent supplemental approvals were based on a determination by FDA that the potential benefits of each product outweighed the potential risks when used for the approved indications according to the directions included in the product labeling. Since approval, additional data regarding the safety and effectiveness of these products have accumulated, in particular new information regarding the potential cardiovascular risks of these products. FDA must consider the impact of these new data on the benefit versus risk profile for each product in making decisions about appropriate regulatory actions.

Although Merck voluntarily withdrew Vioxx from marketing worldwide on September 30, 2004, questions related to Vioxx are included below since it will be necessary for FDA to determine the appropriate regulatory action regarding the approval status of this product.

Based on the data presented in the background package and during the committee meeting, please address the following questions regarding the approved COX-2 selective NSAIDS.

1. Celecoxib
   a. Do the available data support a conclusion that celecoxib significantly increases the risk of cardiovascular events?

      Yes- 32 ***No- 0*** ***Abstain - 0***

b. Does the overall risk versus benefit profile for celecoxib support marketing in the US?

Yes - 31 ***No - 1*** ***Abstain - 0***

c. If yes, please describe the patient population(s) in which the potential benefits of celecoxib outweigh the potential risks and what actions you recommend that FDA consider implementing to ensure safe use of celecoxib.

- ***The Committee agreed that osteoarthritis and rheumatoid arthritis patients, in addition to patients being treated for pain were populations where the benefits of celecoxib could outweigh potential risks. They agreed that there appeared to be no evidence of CV risk at the 200 mg dose and marginally positive evidence at the 400 mg dose. No signal was seen in the epidemiologic studies. With regard to the colon polyp study, 400 and 800 mg doses were studied. An excess CV risk would likely be seen with the 800 mg dose, probable at the 400 mg dose and possibly no evidence with the 200 mg dose.***

  The following were suggested as potential actions for the FDA to take:

  - ***Black Box Warning (BBW) (24)***
  - ***Remove BBW if clinical trial results demonstrate safety (4)***
  - ***Restrict Direct to Consumer Advertising (22)***
  - ***Provide both known and unknown information to patients and health practitioners (22)***
  - ***Develop Patient Guide or Med-guides (25)***
  - ***Provide Dear Health Care Provider Letter (2)***
  - ***Restrict patient population (7)***
  - ***Restrict dose (5)***

2. Valdecoxib
   a. Do the available data support a conclusion that valdecoxib significantly increases the risk of cardiovascular events?

   Yes - 32 ***No – 0*** ***Abstain - 0***

   b. Does the overall risk versus benefit profile for valdecoxib support marketing in the US?

   Yes - 17 ***No - 13*** ***Abstain - 2***

   c. If yes, please describe the patient population(s) in which the potential benefits of valdecoxib outweigh the potential risks and what actions you recommend that FDA consider implementing to ensure safe use of valdecoxib.

In general, the Committee felt that the evidence was very limited and it is difficult to extrapolate to a real life setting.

The following were suggested as potential actions for the FDA to take.

- ***Black Box Warning (22)***
- ***Remove BBW if clinical trial results demonstrate safety (2)***
- ***Restrict Direct to Consumer Advertising (19)***
- ***Provide known and unknown information to patients and health practitioners (19)***
- ***Develop Patient Guide or Medguide (17)***
- ***Dear Health Care Provider Letter (2)***
- ***Restrict population (6)***
- ***Restrict dose (3)***
- ***Restrict duration (6)***
- ***Contraindications in the post CABG setting***

3. Rofecoxib
   a. Do the available data support a conclusion that rofecoxib significantly increases the risk of cardiovascular events?

      Yes - 32 **No - 0** **Abstain - 0**

   b. Does the overall risk versus benefit profile for rofecoxib support marketing in the US?

      Yes - 17 ***No - 15*** ***Abstain - 0***

      The Committee had the following comments:
      - ***The blood pressure effects seen with the product are clearly outside the norm and are undesirable; a mechanism other than a prostacyclin mechanism could be at play since the other COX-2s do not appear to have such a large blood pressure effect***
      - ***A signal for heart failure is present and the other NSAIDs have not exhibited this same signal***
      - ***The blood pressure and the heart failure data is compelling indicating it is substantially worse than other COX-2s***
      - ***A strong dose relationship is very apparent***
      - ***Rofecoxib is the only COX-2 selective product approved for pediatric patients however, there are minimal data to support safe long-term use in pediatrics***

   c. If yes, please describe the patient population(s) in which the potential benefits of rofecoxib outweigh the potential risks and what actions you recommend that FDA consider implementing to ensure safe use of rofecoxib.

The following were suggested as potential actions for the FDA to take:

- ***Black Box Warning***
- ***Remove BBW only if future clinical trial results demonstrate safety***
- ***Restrict Direct to Consumer Advertising (DTC)***
- ***Provide known and unknown information to patients and health practitioners***
- ***Patient Guide or Med-Guides Development***
- ***Dear Health Care Provider Letter***

- ***Require strong Post Marketing follow-up***
- ***Restrict dose to 12.5 mg, 25 mg and remove 50 mg from the market***
- ***Require informed consent***
- ***Provide patient reminders about risk 1 year after starting the drug***
- ***Require clinical trial using 12.5 mg. dose***
- ***Consider restricted access to the drug***
- ***Be aware that the pediatric patient could increase their risk of CV events earlier - but keep for use in pediatric patients because pain is not always adequately controlled***
- ***Institute a patient registry***
- ***Restrict patient population***

4. If the available data support a conclusion that one or more COX-2 selective agents increase the risk of cardiovascular events, please comment on the role, if any, of concomitant use of low-dose aspirin in reducing cardiovascular risk in patients treated with COX-2 selective NSAIDs.

No vote was offered for this question; some of the Committee comments were as follows:

- ***There is insufficient evidence to make a conclusion***
- ***There is no compelling evidence that concomitant low dose aspirin is effective in preventing CV disease when used in "normals"***
- ***Must be careful - ASA is not a panacea for CV disease***
- ***There is no compelling evidence that ASA will reverse CV toxicity based on available studies, but data is limited***
- ***Aspirin appears to "undo" any possible GI benefit of the COX-2s***
- ***If ASA is needed for CV prophylaxis, then patients should not be on a COX-2 inhibitor***

5. What additional clinical trials or observational studies, if any, do you recommend as <u>essential</u> to further evaluate the potential cardiovascular risk of celecoxib, rofecoxib, and valdecoxib? What additional clinical trials or observational studies, if any, do you recommend as <u>essential</u> to further evaluate the potential benefits (e.g., reduced gastrointestinal risk) of celecoxib, rofecoxib, and valdecoxib? Please be specific with regard to which COX-2 selective agent to study, trial design, patient populations, control groups, endpoints, duration, sample size, etc.

No vote was offered for this question; some of the Committee comments were as follows:

- ***Across all products and to rule out the risk of excess cardiovascular events, additional randomized clinical trials (RCT) should be conducted at doses to be marketed; blood pressure measurements should be included in these trials***
- ***Comparator drug used in the trials should not be limited to naproxen; placebo as the comparator should be used in trials designed to determine the absolute risk of CV events***
- ***Choice of comparator would also depend on the population/indication being studied; for example, arthritis trials would not utilize placebo, however pain trials might***
- ***Follow-up of all patients is critical - especially the RCT drop out patients***
- ***It is important that we not ignore the need for additional safety trials with the nonselective NSAIDs***

There are more than 20 non-selective NSAIDs currently approved for marketing in the United States. Unlike the situation with the COX-2 selective agents, large, long-term, placebo-controlled clinical trials have not been conducted to evaluate long-term risks, including cardiovascular risks. Based on the data presented in the background package and during the committee meeting, please address the following questions regarding the approved non-selective NSAIDs:

6. Do you recommend that the labeling for these products include information regarding the absence of long-term controlled clinical trial data to assess the potential cardiovascular effects of these drugs? If so, please describe how you recommend that information be conveyed (e.g., warning, precaution).

   Yes - 28 ***No – 0*** ***Abstain - 0***

(The following members were not present and therefore did not did not offer a vote for question 6: Paganini, Shapiro, Gibofsky, Hoffman)

Committee comments included:

- ***Taking a blanket approach with these drugs is not recommended***
- ***Providing observational data is important with the absence of clinical trial data***
- ***Provide all data so both patients and prescribers are informed on our knowledge level on these drugs***
- ***Although it appears that the CV risk applies to the class as a whole, any BBW should be modified to reflect what we know about each individual product***
- ***Rather than a BBW, some suggest that text be added to the warning section of the label while additional data is collected***
- ***Concern was raised that a BBW may shift patients to meloxicam or other products with even less available risk data; there is no assurance that these products don't have the same risks***
- ***Some indicated that they felt that the available data on naproxen would justify a decreased warning requirement***
- ***It was stated that based on the committee discussions at the AC meeting, a shift in prescribing practice could occur. It is important to send the message that the current state of information is insufficient to state that any of the products are absolutely safe.***
- ***It is important to require that sponsor marketing materials provide the information that is known about their products while at the same time providing adequate information as to what is as of yet unknown about product risk (describe the absence of data)***
- ***The committee advised that caution be used such that revisions regarding long-term use risks to the OTC product labeling does not cause "hysteria"***

7. What additional clinical trials or observational studies, if any, do you recommend as <u>essential</u> to further evaluate the potential cardiovascular risk of the non-selective NSAIDs? Please be specific with regard to which non-selective NSAIDs (i.e., all or only selected agents), trial design, patient populations, control groups, endpoints, duration, sample size, study drug etc.

The Committee comments included:

- ***Randomized Clinical Trials (RCTs) are likely impossible for these products; as an alternative, it was suggested that sponsors conduct large scale, cluster, randomized trials; Randomization to drug would be an important feature to include***
- ***The committee suggested that sponsor incentives could be proposed; These might include deletion of a BBW or warning text should a sponsor design and complete adequate trials.***
- ***The committee agreed that in the absence of "good" safety data, no additional NSAIDs be switched to OTC status***

Standards for approval of new NSAIDs (non-selective and COX-2 selective agents)

The information that has accumulated about the safety and effectiveness of COX-2 selective NSAIDs since their approval, including the potential for increased cardiovascular risk, must be considered as FDA determines the standards for data to be submitted in support of approval of new non-selective and COX-2 selective NSAIDs. In addition, the experience with the approved COX-2 selective agents will help inform benefit versus risk assessments that will need to be made by FDA in evaluating pending and future applications for new NSAIDs.

Based on the data presented in the background package and during the committee meeting, please address the following questions regarding the approval of new non-selective and COX-2 selective NSAIDs.

8. With regard to evaluation of cardiovascular risk, what studies do you recommend as essential to be completed and reviewed prior to approval of new NSAIDs? With regard to the evaluation of the potential benefits (e.g., reduced gastrointestinal risk), what studies do you recommend as essential to be completed and reviewed prior to approval of new NSAIDs? Please be specific with regard to trial design, patient population, control groups, endpoints, duration, sample size, safety monitoring and patient protections, etc.

    - ***It is important to be practical for new drugs to enter the market and they must undertake an APPROVE type of trial in low risk populations and in the active control group - trials must be 1-2 years in length***
    - ***The Committee recommended that future studies include primarily naproxen as a comparator. Ibuprofen and diclofenac should also be studied as comparators for different purposes, ibuprofen as a typical NSAID while diclofenac may be a model of a relatively selective traditional NSAID.***
    - ***Need a neutral or better than neutral, upper confidence boundary against naproxen; the standard/bar needs to be high enough in order to protect the public***
    - ***Suggested populations likely to use the products include those that are older and with a mild CV risk***
    - ***Regarding GI benefit, it would be appropriate to compare new products versus naproxen or another NSAID combined with a PPI***
    - ***The Committee cautioned that recommendations must be practical; trials such as the APPROVe and CABG 2 studies should be conducted in indications sought for marketing, i.e., OA, RA, and low risk individuals (not high risk individuals). The duration of the trials should preferably run two years and include an active control.***

9. If the pre-approval studies recommended as essential in question 8 do not demonstrate an increased risk of cardiovascular events for a new NSAID, please comment on how FDA should handle the issue of cardiovascular risk in labeling. For example, would the absence of a cardiovascular risk signal in the pre-approval database preclude the need for any warnings or precautions in the labeling for the new product? Alternatively, should all future NSAIDs carry a "class" warning or precaution about cardiovascular risk even in the absence of a signal of increased risk in the pre-approval database? If yes, please describe your recommendations for the "class" labeling regarding cardiovascular risk with particular attention to whether you recommend it apply to all NSAIDs or only COX-2 selective NSAIDs.

No vote was offered for this question; The Committee made the following comments:

- ***The absence of establishing an increase risk is not the same as no increase; evidence sufficiently powered and controlled to rule out an increase in incidence is needed***
- ***The Committee consensus was that for new products, the standard for demonstrating safety should be higher***

The meeting was adjourned at 5:15 p.m.

February 2005 Arthritis Advisory Committee Meeting Transcript-

Merck Presentation

(Pages 152-188)

submit that if you were to ask the agency or ask the company on this, if you don't have a good measure on benefit, so you want to make a benefit-risk assessment.

We have measures of risk, they may be imperfect, but I would argue that from a population perspective, you don't really have nearly as good information as you might believe you do from the clinical trials, what the benefit in the population is, how many lives are actually saved by the COX-2s, for example.

DR. WOOD: On that note, I am told the lines are building at the men's room, so we need to be back here at exactly quarter to.

(Recess.)

DR. WOOD: Let's get going.

Arcoxia (etoricoxib)

Merck Research Laboratories

Sponsor Presentation

Sean P. Curtis, M.D.

DR. CURTIS: Mr. Chairman, members of the Joint Advisory Committee, FDA, ladies and

gentlemen: My name is Dr. Sean Curtis, Senior Director, Clinical Research, at Merck and Company, and I would like to thank you for the opportunity to review data from the Etoricoxib Development Program.

I believe the committee will find these data informative and contribute to the further evaluation of this therapeutic class, a goal we all share collectively.

Drs. Konstam and Loren Laine are serving as consultants today and are available as a resource to the committee.

Following an introduction, results from the development program will be summarized beginning with efficacy, followed by a review of the safety findings. I will first review the gastrointestinal and renovascular safety, followed by thrombotic cardiovascular safety.

I will then review the design of three studies, which together are designed to further characterize and assess the cardiovascular safety of etoricoxib in arthritis patients.

Cardiovascular safety data from the first of these three studies, the EDGE study, will be reviewed, and I will conclude with a summary.

My presentation will focus on the following points. Etoricoxib, as a selective COX-2 inhibitor, has a role among the current treatment options for patients with diseases and conditions characterized by pain and inflammation.

Supportive data will be reviewed, namely, efficacy that has been demonstrated to be similar and, in some cases, superior to NSAIDs, specifically naproxen 1,000 mg; gastrointestinal safety and tolerability, favorably differentiated from NSAIDs; and a renovascular safety profile, which is dose dependent and generally similar to the effects observed with comparator NSAIDs at therapeutic doses.

With regards to thrombotic cardiovascular safety, cardiovascular events occurred at a similar rate on etoricoxib as compared to non-naproxen NSAIDs over the course of approximately 1 year. Data are currently limited beyond 1 year of

treatment, and events occurred at different rates in comparison to naproxen.

The other key point for my presentation is that large, randomized clinical trials are currently ongoing to further characterize the long-term cardiovascular safety of etoricoxib as suggested by many members of this joint committee.

These results will provide a full characterization of the cardiovascular safety profile of etoricoxib in arthritis patients as compared to diclofenac.

These data are critical to the current scientific debate over cardiovascular safety. Specifically, we will address whether the long-term cardiovascular safety of a selective COX-2 inhibitor is similar to, or different, than that of a traditional NSAID.

Let's begin reviewing the data.

Etoricoxib represents a distinct chemical entity. It consists of a bipyridine ring with methyl sulfone side chain. In the clinical dose range, etoricoxib has demonstrated selectivity for

the COX-2 enzyme using human whole blood biochemical assays.

Its absorption is rapid with a peak plasma concentration achieved by approximately 1 hour and with an effective half-life of approximately 22 hours, it is suitable for once daily dosing.

Etoricoxib is currently approved in approximately 60 countries. Core indications include osteoarthritis at a once daily dose of 60 mg, rheumatoid arthritis at a once daily dose of 90 mg, and acute gouty arthritis. The dose is 120 mg for the acute symptomatic period only.

In the United States, the FDA issued an approvable action on our new drug application.

I would now like to summarize efficacy. The efficacy of etoricoxib has been demonstrated across a range of conditions and diseases characterized by pain and inflammation.

For these conditions, efficacy data have been published or accepted for publication including 3 diseases and conditions for which an indication is not currently granted in the United

States for a selective COX-2 inhibitor. These include studies in chronic low back pain, ankylosing spondylitis, and acute gouty arthritis.

As you will remember, the acute gouty arthritis data were discussed with the Arthritis Advisory Committee in June 2004 in the context of a committee meeting design to look at gout study designs.

Efficacy data are summarized in your background package, however, I would like to draw your attention to results obtained in three specific disease models.

The rheumatoid arthritis program included 2 pivotal double-blind, placebo and active comparator- controlled studies in approximately 1,700 patients. In one study, etoricoxib 90 mg demonstrated efficacy that was statistically superior to naproxen 1,000 mg for all primary endpoints and all additional endpoints including the ACR20.

In the other study, etoricoxib demonstrated efficacy that was similar to naproxen,

and in patient with the ankylosing spondylitis, we performed a single pivotal double-blind, placebo and active comparator-controlled study which enrolled approximately 390 patients.

Over the 52-week treatment period, etoricoxib demonstrated efficacy that was statistically superior to naproxen 1,000 mg for all 3 co-primary endpoints, and in patient with acute gouty arthritis, we performed 2 double-blind, active comparator-controlled studies enrolling approximately 350 patients in total.

In those studies, etoricoxib at a dose of 120 mg for 7 days demonstrated efficacy that was comparable to indomethacin.

I would now like to begin reviewing the safety data.

The gastrointestinal safety program, as summarized in your background package, was designed to evaluate the entire GI tract. Clinical outcomes based on pooled data from the entire development program were prespecified for analysis. These include a combined analysis of upper GI clinical

events, or PUBs, and a combined analysis of GI tolerability.

Here are summarized results from the prespecified combined analysis of upper GI clinical events which occurred in Phase IIB and III studies from the entire development program by displaying the cumulative incidence of confirmed events by treatment group over the entire duration of the studies involved in the analysis.

As you see, a statistically significant relative risk of 0.48 favoring etoricoxib was demonstrated. This represents a 52 percent risk reduction. It was observed early and maintained over the entire study duration. These results are largely driven by comparisons to naproxen.

For purposes of summarizing renovascular safety, we will focus on data from the osteoarthritis and the rheumatoid arthritis studies, which represent the majority of the data. Presenting results by disease types ensures the patient characteristics are similar among the treatment groups.

This slide displays the incidence of hypertension adverse experiences by treatment group observed over a 12-week treatment period, in OA

patients on the left, and RA patients on the right.

In the OA population, the dose response is observed most clearly from 30 to 60 and 60 to 120 mg, 90 mg is outlying likely due to the smaller sample size, and in the RA population, the dose response is also observed although less evident as compared to osteoarthritis.

Overall, the rates observed for etoricoxib, specifically the doses indicated for chronic use, that is, 60 and 90, are within the range observed with comparator NSAIDs, numerically higher than naproxen, numerically lower than that observed with ibuprofen, and in both patient populations, it was rare for patients to discontinue from this adverse experience with no clear difference observed between treatment groups.

In addition to hypertension, we looked closely at adverse effects related to edema and congestive heart failure. Tabulated here are the

incidence of congestive heart failure adverse effects as spontaneously reported by investigators in our placebo-controlled population of up to 12 weeks duration.

As you see here, incidences are low among the active treatment groups. I would like to show you the cumulative incidence of congestive heart failure adverse events which occurred over the entire duration of our chronic exposure studies.

We see here that etoricoxib as compared to comparator NSAIDs pooled are associated with similar rates of congestive heart failure adverse events. The grouping of terms is indicated on the bottom of the slide.

The data provided in your background package and summarized thus far support the improved gastrointestinal safety and tolerability of etoricoxib compared to non-selective NSAIDs, with clinical outcomes data including PUBs and GI intolerance endpoints, as well as endoscopic data.

These data also provide evidence of the renovascular profile of etoricoxib, that is,

hypertension, edema, and heart failure are dose related as would be expected, and generally similar to the effects observed with comparator NSAIDs, in some cases numerically higher and in some cases numerically lower.

I would now like to move on to cardiovascular safety data review. The process that Merck instituted for prospectively adjudicating all potential thrombotic events as described by Dr. Braunstein yesterday for rofecoxib, was operative for etoricoxib from the beginning of Phase IIB.

We prespecified an analysis of all such events using individual patient data from studies of at least 4 weeks in duration across the clinical development studies.

In total, there were 12 studies included in this analysis including approximately 6,700 patients and 6,500 patient years of exposure. For the analysis, comparisons of etoricoxib were made to placebo or active comparator NSAID using data only from the studies that contained the treatments

being compared.

The etoricoxib group and analysis you will be seeing shortly consists of data combined from doses of 60, 90, and 120 mg in order to improve statistical precision, and for the comparison to NSAIDs, naproxen was compared to etoricoxib separate from the other 2 NSAIDs, diclofenac and ibuprofen, based on the fact that naproxen is distinct pharmacodynamically from both ibuprofen and diclofenac, and because qualitative differences were observed in the comparison to naproxen versus the comparison to non-naproxen NSAIDs.

The endpoint specified as primary for the assessment of cardiovascular safety in the etoricoxib development program was a composite endpoint of all confirmed thrombotic events confirmed by the Adjudication Committee, and includes cardiac, cerebrovascular, and peripheral vascular events.

The primary results for the pooled analysis are summarized here by presenting the point estimate of the relative risk and the

corresponding 95 percent confidence interval for the comparisons of etoricoxib to placebo, to non-naproxen NSAIDs, and to naproxen for the composite primary endpoint of confirmed thrombotic events.

The naproxen-controlled data set is the largest of the 3 data sets, and the placebo-controlled data is the smallest of the 3. This is indicated numerically on the right in patient years at risk and correspondingly reflected by the size of the triangle representing the point estimate of the relative risk.

When comparing etoricoxib to placebo and to non-naproxen NSAIDs, the relative risk approximates 1.0 indicating no discernible difference in thrombotic cardiovascular events between those treatment groups.

However, it is important to keep in mind that the maximum duration of the placebo-controlled period was 12 weeks, and when comparing etoricoxib to naproxen, the relative risk is greater than 1, indicating a difference between the 2 treatment

groups in a trend favoring naproxen in that comparison.

Shown here are the cumulative incidence of confirmed thrombotic events in the non-naproxen-controlled data set. The amount of data are limited at longer term time points particularly for the non-naproxen NSAID group.

In total, the event rates are similar between treatment groups.

All individual events were categorized by the Adjudication Committee as either cardiac, cerebrovascular, or peripheral vascular. In reviewing the specific events in the non-naproxen-controlled data set, using this categorization, cardiac and cerebrovascular events were observed in both treatment groups.

Numeric differences between treatment groups trended in both directions and were observed at the level of individual events.

As indicated previously, the largest of the 3 data sets is the data set which compares etoricoxib to naproxen. As you can appreciate from

these cumulative incidence curves, the etoricoxib and naproxen groups separate early with a lower cumulative incidences observed on naproxen as compared to etoricoxib.

In the naproxen-controlled data set, the specific confirmed thrombotic events occurred in all 3 vascular events. In considering the overall difference between the naproxen-etoricoxib group, no single event predominates, however, a higher incidence of ischemic cerebrovascular strokes was observed on etoricoxib in this comparative data set.

Analyses were performed to explore the relation between dose of etoricoxib and rate of thrombotic events. The left two panels summarize the results of a pair-wise analysis, an approach that includes data only from studies that contained the doses being compared.

The righthand panel represents results using a summary approach, which incorporates rates by dose from all studies in the pooled cardiovascular analysis.

The data do not indicate evidence of a dose effect across the 60 to 120 mg etoricoxib dose range.

Summarized in your background package are results of subgroup analyses from the naproxen-controlled data set including patients at increased baseline cardiovascular risk and by arthritis disease type particularly OA versus rheumatoid arthritis.

These subgroup analyses, as well as additional analyses including those subgroups identified to be potentially at increased risk based on the rofecoxib APPROVe study failed to identify any specific patient subgroup at increased relative risk for thrombotic event.

It is important to remember, however, that the amount of etoricoxib cardiovascular safety data currently available do not allow us to make firm conclusions for any specific subgroup.

All-cause mortality in the etoricoxib development program is summarized here as rates per 100 patient years by treatment group. Included, as

well, are results from the EDGE study, a study of approximately 1 year's duration in over 7,000 osteoarthritis patients comparing the GI tolerability of etoricoxib to diclofenac.

Rates for etoricoxib and non-naproxen NSAIDs in the left panel are similar and numerically higher than those observed on naproxen and placebo, which are similar to each other. The rates here are represented as a point estimate with a corresponding 95 percent confidence interval.

As you see, the confidence intervals are broad and overlapping between the treatment groups. Based on these data, there is no evidence for a true difference in all-cause mortality between treatment groups.

In the EDGE study, on the right, rates were numerically similar between treatment groups in all-cause mortality again with confidence intervals that overlap the point estimates between treatment groups, at this point indicating no evidence of a difference.

The cardiovascular safety data from the

original development program can thus be summarized as follows. There is no clear evidence of a difference between etoricoxib and placebo based on limited amounts of short-term data.

There is no discernible difference in cardiovascular event rates between etoricoxib and non-naproxen NSAIDs. This comparison is limited, however, by the amount of active comparator-controlled data with both diclofenac and ibuprofen, and naproxen, at a regimented dose of 500 mg twice daily is associated with a lower rate of thrombotic events as compared to etoricoxib.

As you saw from the Kaplan-Meier curves, the cumulative incidences, a difference, separates early, and is, in fact, this is an observation that has been seen with the rofecoxib data and similar to the observations made from the lumiracoxib TARGET study, which we will be hearing about later.

Recent results from long-term placebo-controlled studies with rofecoxib and celecoxib have important implications for etoricoxib. Specifically, these recent data

showing a difference in cardiovascular safety in long-term studies versus placebo do, in fact, suggest a class effect.

Despite the large size of the original development program, over 10,000 patients, approximately 5,800 of which were receiving etoricoxib, there are limitations on the amount of accrued cardiovascular safety data. Specifically, the long-term data were limited in quantity, and limited primarily in comparison to naproxen.

Because of questions raised with respect to naproxen, we decided we needed a different approach to accrue additional data, and I would now like to review the strategic approach we took and then discuss the specific studies that resulted.

Our primary objective was to further establish the long term general and cardiovascular safety of etoricoxib in arthritis patients who required treatment. At the time the strategy to meet this objective was formulated, there were ongoing long-term placebo-controlled studies with other selective COX-2 inhibitors, largely focusing

on exploring novel indications for cyclooxygenase-inhibiting therapies. Examples include Alzheimer's disease and chemoprevention.

For etoricoxib, rather than explore novel indications with placebo-controlled studies, we chose to further evaluate the group of patients who required treatment for arthritis. Therefore, the plan we developed was to perform active comparator-controlled studies in osteoarthritis and rheumatoid arthritis patients.

Studying this patient population ethically precluded use of a placebo for more than a short period of time, because these patients require active treatment. Diclofenac was chosen as the active comparator, and I will review our rationale for that choice shortly.

Although the recent study results with rofecoxib and celecoxib were not available when we designed the studies that I will be describing shortly, our studies are extremely relevant as they compared etoricoxib to diclofenac and thus address the current clinical question of comparative

cardiovascular safety between a selective COX-2 inhibitor and a traditional NSAID.

In order to choose an appropriate comparator NSAID, we established criteria and evaluated numerous agents and ultimately determined that diclofenac was the most suitable choice.

Diclofenac is effective in treating both osteoarthritis and rheumatoid arthritis patients and can be dosed twice daily, which enhances compliance and convenience for the patient.

Secondly, it has been established that diclofenac does not interfere with low-dose aspirin's anti-platelet effects. Ibuprofen, on the other hand, does interfere with low-dose aspirin's anti-platelet effects.

This interaction posed two issues we felt precluded use of ibuprofen as the comparator. We were not comfortable enrolling patients who required low-dose aspirin with knowledge that its anti-platelet effects could, in fact, be inhibited, and secondly, we were concerned that interpretation of study results, which showed comparable

cardiovascular safety, to an agent that inhibits aspirin's anti-platelet effects could be problematic.

Diclofenac inhibits both COX-1 and COX-2 and confers partial inhibition on platelet-mediated COX-1 thromboxane. Since it lacks potent and sustained anti-platelet activity, we would not expect confounding effect on the interpretation of cardiovascular safety results as would be expected with naproxen based on the cardiovascular data from the development program which I presented.

Data from some of our clinical trials indicate that diclofenac's effect on blood pressure is generally similar and, in fact, in some cases more pronounced than the effect observed with etoricoxib.

In consideration of the established cardiovascular complications of elevations in blood pressure, a comparison of thrombotic cardiovascular safety between etoricoxib and diclofenac can, in fact, be considered conservative.

I wanted to briefly review some

pharmacodynamic data which supports diclofenac having COX-1 inhibiting effects. Represented on this slide are the ex-vivo COX-2 and COX-1 inhibiting effects of various agents.

Displayed on the X axis is the percentage of COX-2 inhibition as measured by inhibition of lipopolysaccharide-induced serum PGE 2. Displayed on the Y axis is the percentage of COX-1 inhibition as measured by serum thromboxane as a weighted average at steady state with 84 percent joint confidence regions around the point estimate of the mean.

Rofecoxib at 12.5 and 25 mg inhibits COX-2 on the order of 60 to 70 percent in this experiment. Diclofenac at a dose of 150 mg inhibits COX-2, but also inhibits COX-1.

Endoscopic data are also available which support the COX-1 inhibiting effects of diclofenac. Shown here are results from two endoscopy studies performed with valdecoxib which included a diclofenac treatment arm. In each case, the cumulative incidence of gastroduodenal ulcerations

observed at the end of the study period are displayed by treatment group in these two studies.

On the left are results of a 26-week study of rheumatoid arthritis patients. The incidence of gastroduodenal ulcerations observed on diclofenac was significantly greater than observed on either dose of valdecoxib in this study.

On the right are results of a 12-week study in osteoarthritis patients. The incidence of gastroduodenal ulcerations on diclofenac was significantly greater than placebo and valdecoxib, and, in fact, similar to the incidence observed on ibuprofen.

Lastly, I would like to point to some GI clinical outcomes data which also support the COX-1 inhibiting effects of diclofenac. Dr. Braunstein reviewed the cumulative incidence of confirmed upper GI clinical events of rofecoxib versus individual NSAIDs yesterday based on final data from the rofecoxib development program.

What I have done here is instead of looking at confirmed PUBs, I have also added the

confirmed plus unconfirmed results, which are very consistent with what Dr. Braunstein showed yesterday.

You see here the relative risk of confirmed plus unconfirmed upper GI events observed on rofecoxib is, in fact, significantly different than the effect observed with diclofenac, so again to provide some clinical data that support a COX-1 inhibiting effect of diclofenac.

The overall approach to further characterize etoricoxib that I have been describing consists of a prospectively designed analysis of cardiovascular safety data will accrue from three studies, which I am going to briefly review here.

All three studies compared etoricoxib to diclofenac. The first is the EDGE study, a study of 7,111 osteoarthritis patients with a primary objective to compare the GI tolerability of etoricoxib to diclofenac. This study is now complete.

Secondly, EDGE II, a study of approximately 4,090 RA patients with a primary

objective identical to that of EDGE. The dose of etoricoxib in EDGE II is 90 mg. This study is fully enrolled and ongoing. The predicted mean duration of this study is expected to be approximately 19 months.

Thirdly, MEDAL, a study of approximately 23,450 osteoarthritis and rheumatoid arthritis patients with the primary objective of comparing the cardiovascular safety of etoricoxib to diclofenac. This is an endpoint-driven outcome study. MEDAL is fully enrolled and currently ongoing. The predicted mean duration of therapy in MEDAL is approximately 20 months with some patients expected to be on therapy an excess of 3 years.

Although EDGE and EDGE II are designed as primary GI tolerability studies, the cardiovascular safety data that will accrue from those two studies are being adjudicated and will be combined with the cardiovascular safety data from the MEDAL study in order to improve the precision of the comparison.

The primary hypothesis for this analysis is that etoricoxib will demonstrate a

cardiovascular safety profile that is non-inferior to that of diclofenac. There are 2 key analyses that are designed to support this hypothesis.

The primary analysis will consider the minimum required 635 confirmed thrombotic events from all 3 studies combined, and the secondary analysis will consider the minimum 490 confirmed thrombotic events that are required from the MEDAL study alone.

As I mentioned, MEDAL was designed as an endpoint-driven outcome study and on its own represents a sufficiently powered assessment of cardiovascular safety. The patient population that has been enrolled in these studies consists of patients with a range of baseline cardiovascular risk and includes patients with pre-existing cardiovascular disease.

As clinically indicated, such patients, as well as others, are being prescribed aspirin, so we expect the total study cohort to include approximately 30 percent aspirin users.

MEDAL and EDGE II will generate a

tremendous amount of long-term cardiovascular safety data. As summarized on the previous slide, the predicted mean duration of therapies in EDGE II and MEDAL are 19 and 29 months respectively, and it is predicted that out of the 635 confirmed thrombotic events, approximately 200 of those events will occur in patients who have been on study therapy for at least 18 months.

In this cohort alone, the minimum between treatment group difference that would be statistically significant expressed as a relative risk is approximately 1.3.

An external Data and Safety Monitoring Board was chartered to monitor emerging data from MEDAL, EDGE, and EDGE II. Since 2002, they have been meeting regularly, most recently in November of 2004, at which time they reviewed a large amount of data. At that time, in total, there were approximately 21,000 patient years of exposure and approximately 300 confirmed thrombotic events were available at that time for their review.

In addition, there were approximately

3,000 patients who had been on study therapy for at least 18 months at that time. Based on their review, their recommendation was to continue the ongoing studies without interruption or without modification.

Of the 3 studies that we have been discussing, EDGE is the first to be completed, and I would now like to review the cardiovascular safety data from the EDGE study.

In this study, the 7,111 osteoarthritis patients were on study therapy for a mean duration of approximately 9 months, resulting in approximately 5,400 patient years of total exposure.

The study population included patients with a range of baseline cardiovascular risk. Here are summarized some selected baseline characteristics. As you see, approximately 38 percent of the patients in this study were at increased baseline cardiovascular risk defined as patients having 2 or more risk factors for cardiovascular disease or a documented history of

symptomatic atherosclerotic cardiovascular disease.

This slide summarizes the cardiovascular safety data from the EDGE study by presenting again the point estimate of the relative risk and the corresponding 95 confidence interval, for confirmed thrombotic events versus diclofenac, for events which occurred on therapy or within 14 days of study therapy discontinuation, on study therapy or within 28 days, and importantly, an all patients treated analysis.

In the EDGE study, all patients who discontinued were followed up closely with regular phone contact to ascertain any events that occurred long term off-of-study therapy, and this was done for all patients until all patients had completed the study.

The cumulative incidence of confirmed thrombotic events in the EDGE study are summarized here, and indicate no evidence of a difference between the treatment groups over time.

This slide summarizes the specific confirmed events by type in the EDGE study

beginning with events which occurred on study therapy or within 14 days of discontinuing study therapy.

As you see, there are events reported in all 3 vascular events with more cardiac event overall irrespective of treatment group. Evaluation of individual event types indicates that the absolute number of any event was small with numeric differences between treatment groups for certain events with some occurring at a higher rate on etoricoxib and some occurring at a lower rate.

For example, differences were observed in ischemic strokes numerically favoring etoricoxib, however, differences favoring diclofenac were observed for acute myocardial infarctions. Neither of these differences were statistically significant.

It is important to remember that even in a study of this size, results at the level of individual events should be interpreted cautiously. For example, when looking at events which occurred on study therapy or within 28 days, as requested by

the agency, the numeric differences between treatment groups has, in fact, narrowed slightly due primarily to an increase in the number of acute myocardial infarctions which occurred on the diclofenac group.

Data from ongoing randomized clinical trials will be critical to more precisely assess the comparative rates of myocardial infarctions on diclofenac versus etoricoxib.

Summarizing results of the EDGE cardiovascular safety data next to the results of the pooled analysis that I presented previously indicate that the EDGE data are, in fact, consistent with, and add precision to, the observations from the pooled analysis when comparing etoricoxib to non-naproxen NSAIDs.

I would now like to summarize. We have demonstrated efficacy with etoricoxib that is similar and in the cases I have pointed out, in fact, superior to comparator NSAIDs particular naproxen 1,000 mg.

We have a GI safety program that did

demonstrate improved GI safety and tolerability in relation to shift to non-selective NSAIDs primarily in relationship to naproxen, and the renovascular effects observed with etoricoxib are, as again would be expected based on the mechanism of action dose related, but at the doses recommended for chronic use are, in fact, generally similar to the effects observed for the comparator NSAIDs.

We saw numeric differences against naproxen favoring naproxen, but we also saw rates of hypertension that were very similar to those observed with ibuprofen even at their maximal chronic dose.

Based on thorough and ongoing reviews of cardiovascular safety data, there is no clear or discernible difference between etoricoxib and non-naproxen NSAIDs up to a year. As I said, we have limited amounts of data beyond 1 year at this time.

Differences were observed between etoricoxib and naproxen rates of thrombotic events. Based on the data we have, the limited amounts of

short-term placebo data, there is no clear difference between etoricoxib and placebo. That being said, emerging data from long-term placebo-controlled studies with rofecoxib and celecoxib showing a difference in cardiovascular safety versus placebo do, in fact, suggest a class effect.

MEDAL, the largest NSAID trial known, and EDGE II are currently ongoing and based on current cardiovascular event rates are expected to be completed next year. Results from these studies will further characterize the cardiovascular safety of etoricoxib, and we will have data to address numerous questions including cardiovascular safety in both osteoarthritis and rheumatoid arthritis patients, and cardiovascular safety in patients with a range of cardiovascular risk, and will include experience in aspirin users and non-users.

We will be able to further explore the effect of dose as both 60 and 90 mg are included in the study, and perhaps, most importantly, the long-term cardiovascular safety will be assessed as

we will have large amounts of data in patients who have been on study therapy for at least 18 months.

These studies directly address whether the cardiovascular safety including the long-term safety of a selective COX-2 inhibitor, such as etoricoxib, is similar to or different than that of a traditional NSAID.

In countries where etoricoxib is currently approved, Merck has consistently taken a proactive approach with regulatory agencies. From the time it was first approved years ago, the etoricoxib product label has, in fact, contained a precaution for use in patients with ischemic heart disease.

We continue to work aggressively with regulatory agencies and are currently actively engaged with European regulators, and have participated in a referral process in Europe. Our goal there is to ensure that the product label accurately reflects all accruing safety information that is relevant to prescribers based on data that are currently available.

In conclusion, etoricoxib has a role among

the current treatment options for patients with conditions characterized by pain and inflammation. However, it is critical to ensure its safe and effective use, that a product labeling continues to be revised to ensure that all currently available data are incorporated to help guide appropriate use.

We remain committed to help address public health questions and currently, with etoricoxib, largely through the conduct of the MEDAL and the EDGE II studies. These questions posed yesterday include, For patients who require chronic anti-inflammatory therapy for established indications, what is the risk and benefit of a selective COX-2 inhibitor as compared to an NSAID?

MEDAL and EDGE II will provide information to this question in comparison to diclofenac, and I have provided you the data we currently have available that provides information relative to naproxen.

Other questions which remain at this time include Can patients at increased cardiovascular

risk be identified, so the benefit is maintained and the risk minimized?

MEDAL, again due to its unparalleled size, and with the additional data from EDGE II, will provide information and data to allow further exploration to help answer this question.

Next, Is the increased cardiovascular risk a class effect of COX-2 inhibition, and if so, how large is the class, and what are the long-term cardiovascular effects of a selective COX-2 inhibitor and traditional NSAIDs?

Again, MEDAL, with its long-term direct comparison to diclofenac, will provide information to address both of these questions.

This concludes my presentation. I would like to thank the Chairman, members of the Advisory Committee, the FDA.

Thank you.

DR. WOOD: Thanks a lot. Let's go straight on to the FDA's presentation.

FDA Presentation

Analysis of Cardiovascular Thromboembolic Events with Etoricoxib

Joel Schiffenbauer, M.D.

DR. SCHIFFENBAUER: Thank you and good

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FDA Presentation

(Pages 188-201)

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FDA Presentation

Analysis of Cardiovascular Thromboembolic Events with Etoricoxib

Joel Schiffenbauer, M.D.

DR. SCHIFFENBAUER: Thank you and good

morning. My name is Joel Schiffenbauer. I am going to be presenting an analysis of cardiovascular thromboembolic events with etoricoxib.

I will be presenting the results of trials for the following indications listed here in the NDA. In addition, I will be presenting results of the EDGE trial separately from those of the trials here.

I will first present briefly exposure data followed by mortality data and then spend the remainder of the time discussing the cardiovascular thromboembolic events data. Again, I will present data first for the NDA and separately for the EDGE study.

First, exposure. This slide summarizes the chronic exposure to etoricoxib across the NDA. As you can see for the 60, 90, and 120 mg doses, which were the proposed doses for the drug, the

total number of patients is shown here and the mean number of days is shown here.

For the EDGE study, there was approximately 3,500 patients in each arm, exposed for a mean of 9 months. Total patient years is shown at the bottom.

Let me turn now to the mortality data. This is the mortality data across the NDA. Rates are shown as per 100 patient years, and I have listed the comparators here, placebo, non-naproxen nonsteroidals, and naproxen.

If we first look at the first line of total deaths, we can see that the rate of deaths in the placebo group is similar to naproxen, followed by the non-naproxen nonsteroidals, and then etoricoxib.

Let me next draw your attention to the third line, thrombotic cardiovascular deaths. There were no deaths in the placebo group, followed by naproxen, etoricoxib, and then non-naproxen nonsteroidals.

These 2 events I would point out occurred

at greater than 36 months exposure to the non-naproxen nonsteroidals, and I will come back to this point when I present the Kaplan-Meier analysis looking at non-naproxen nonsteroidals.

The deaths in the EDGE study, the total deaths are similar, 8 and 6, for cardiovascular thrombotic related, it was 3 and 1.

Let me now move on to a discussion of the cardiovascular thromboembolic events.

The sponsor proposed a composite endpoint, which you have already heard about, which included events related to the cardiac, peripheral, and cerebrovascular system. I will present results for both the composite, as well as the components of the composite, and I think this is an important point because we do not yet know the effects of COX-2 inhibitors on each of these specific cardiovascular events.

In addition, I will not present data for APTC events or investigator-reported events. Although the numbers vary slightly, the trends are always in the same direction as the events that I

will show here.

These events were referred to an Adjudication Committee, that you have heard about already, and after being reviewed in that committee, were then described as confirmed cardiovascular thromboembolic events.

This slide shows an analysis of the confirmed thrombotic cardiovascular serious adverse events across the NDA. This is exclusive of the EDGE study. The sponsor performed 3 comparisons - etoricoxib to placebo, etoricoxib to non-naproxen nonsteroidals, and etoricoxib to naproxen.

The number of patients, the cases in patient years of exposure is shown here, rates, and relative risk. I will show this slide over again.

First, let me start on the first line. I draw your attention to the rate of events in the etoricoxib group 1.25 versus placebo 1.19 for the relative risk shown here, and an analysis of those events is shown in this slide.

These are the rates I showed you, 1.25 and 1.19. There were a total of 7 patients in the

etoricoxib group versus 4 in placebo, and this breaks down to 4 cardiac events, which are listed here - MI, fatal MI, unstable angina, and sudden death versus zero in placebo.

The number of events in peripheral and cerebrovascular are similar although the rates do vary slightly.

Let me point out here that in some of these slides, these numbers will not necessarily add up. That is for two reasons. One is an individual patient may have more than one event, and they would therefore be listed in more than one category, and, secondly, for the sake of clarity and brevity, I left out in some instances all the events.

This is the Kaplan-Meier estimate of time to event for the placebo comparison. Note that this is only 3 months in duration. There are very little differences between the two groups.

Let me move on then to the etoricoxib/non-naproxen comparisons. Here is the rate, 0.79 and 0.80, and I will show you that in

next slide. Here are the rates again, 0.79 and 0.80. These are composed of 12 patients in the etoricoxib group versus 4 in the combined, and by that I mean combined exposure to diclofenac and ibuprofen. You can see, however, exposure to ibuprofen is rather small and there were no events, so all of the events come from the diclofenac exposure.

If we examine the breakdown of these 12 events, you can see there were 11 cardiac events in the etoricoxib group for the rate shown here versus 2 in the combined for this rate, and that is further broken down to 3 MIs versus zero, 2 and 1 of fatal MIs, and then the rest you can see here. There are 2 and 2 events in the cerebrovascular system.

You have seen this previously, but let me make several points about this Kaplan-Meier analysis for the non-naproxen and nonsteroidal comparisons. First of all, you will note that the length of exposure is out to 36 months when there are relatively few patients still present in the

studies.

Secondly, there were 4 events in the non-naproxen nonsteroidals, which is shown by the solid line. Three of those events occurred at greater than 36 months exposure. Two of those 3 events were the deaths that I described in the earlier slide.

In contrast, there were 12 events in the etoricoxib group, 11 out of those 12 events occurred at approximately 26 months or earlier. So, there is a difference in the time to event as demonstrated by this Kaplan-Meier analysis.

Lastly, let me turn to the etoricoxib/naproxen exposure. Here are the rates, 1.37 and 0.81. Again, here are the rates, 1.37 and 0.81. There were 34 patients in etoricoxib versus 14 in naproxen, and that is broken down into 21 cardiac versus 9 for the rate shown here, 10 MIs versus 5, and you can see the remainder.

For peripheral, there was a slight imbalance, 5 events in naproxen versus 2 in peripheral, however, when we come back to the

cerebrovascular system, there were 12 versus 2, which included 10 ischemic strokes versus zero. Again, you have seen the Kaplan-Meier analysis, which shows a separation of the two curves almost throughout the entire exposure.

Let me turn now to the analysis of cardiovascular events in the EDGE study, and start by making a few points. There were 7,100 patients. It was designed as a GI tolerability study in which cardiovascular data was collected.

The sponsor defined a non-inferiority margin to diclofenac for cardiovascular events as the upper limit of the 95 percent confidence interval for the hazard ratio of 1.3.

In addition, there were several concerns that I would like to emphasize. First, it was designed as a non-inferiority trial, there was no placebo. Diclofenac was the only comparator, and as we have heard here, and there is data in the literature to support the relative COX-2 selectivity of diclofenac.

Next, there were only osteoarthritis

patients studied. There were no rheumatoid arthritis patients in this study. We know that rheumatoid arthritis itself confers cardiovascular risk.

The next two bullets relate to maneuvers that could potentially, in the context of a non-inferiority trial, make it difficult to identify differences between the two treatment groups.

So, for example, there was 30 percent aspirin use. If we believe that aspirin is cardio-protective even in the context of COX-2 inhibitor, this could make it difficult to discern any differences between the two groups.

In addition, previous COX-2 use was allowed, and I have listed here what that was, and this could potentially lead to depletion of susceptible individuals to a cardiovascular event.

Lastly, although it is important to study high-risk patients, if these high-risk patients are on aspirin, that may be a problem in differentiating the two groups. In addition, if

there are more events in these high-risk patients, it could increase the background events, and again in the context of a non-inferiority trial, may make it difficult to differentiate the two treatment groups.

So, you have seen this Kaplan-Meier analysis. Again, the two groups separate slightly, but the two curves do finally converge at approximately 12 months.

This is a breakdown of the events in the EDGE trial. There were 35 patients in the etoricoxib group versus 30 in diclofenac for the rates given here. If we look at a further breakdown of the components, we see there were 27 cardiac-related events versus 19 for the rates given here. For MI, there was 19 versus 11. For cerebrovascular events, there was 7 and 7 with a slight imbalance in ischemic strokes of 6 in diclofenac versus 3 in etoricoxib.

I think it is important, I mentioned earlier that aspirin use may be a problem. I broke down the number of events by aspirin and

non-aspirin users, and I have just provided the number of events, the patient years of exposure are fairly similar.

You can see that by aspirin users, there is little differences between the groups, 12 versus 9 here for cardiac events, 7 and 5. However, when you look at the non-aspirin users, the differences are more pronounced. There were 15 cardiac events in etoricoxib versus 10 in diclofenac, and 12 MIs versus 6.

There was some concern about hypertension. Some issues were raised about that yesterday. I show some data for hypertension-related adverse events in the EDGE trial. These types of adverse events could include anything from a hypertensive crisis, malignant hypertension to systolic blood pressure increase among other events.

This is an analysis of patients with serious hypertension-related adverse events. There were 5 in etoricoxib versus 2 in diclofenac, and then another category, hypertension-related AE associated with systolic blood pressure greater

than 180, or diastolic greater than 110, and there were 69 cases here versus 30 in diclofenac.

Then, this is a cumulative incidence of new use of anti-hypertensive medications. The upper line is etoricoxib, the lower line is diclofenac. You can see that the two curves separate almost throughout the entire 12-month period.

Lastly, a description of congestive heart failure-related adverse events. This is the incidence of CHF pulmonary edema-related or cardiac failure adverse events. There were 14 versus 6.

In summary, in the NDA, etoricoxib trends worse in terms of cardiovascular thromboembolic events, particularly cardiac and MI. The one common thread throughout all the comparators does appear to be the cardiac system.

There are differences in the cerebrovascular or peripheral system, but those are inconsistent depending on the comparator.

Comparisons of etoricoxib to naproxen for the cardiovascular events is similar to what you

have seen for rofecoxib and the naproxen comparisons.

I have outlined some trial design concerns in the EDGE study, which I presented, and as you have already heard, there are two ongoing trials of similar design, which I believe have similar concerns.

There are trends in the EDGE study for cardiac events, worse for etoricoxib, and that is seen mainly in the non-aspirin users.

Thank you.

DR. WOOD: Thanks very much.

Let's go straight on to the Novartis talk and we recognize that will finish a little late, but we will have a shorter lunch break.

Lumiracoxib

Lumiracoxib: Introduction

Novartis Pharmaceuticals Corporation

Sponsor Presentation

Mathias Hukkelhoven, Ph.D.

DR. HUKKELHOVEN: Thank you.

Dr. Wood, Dr. Gibofsky, Dr. Gross, members

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Panel Discussion

(Pages 347-387)

It is just after five past 3:00, and we need to get started on that.

Let's begin with the questions for the speakers on etoricoxib.

Oh, Dr. Hennekens first.

DR. HENNEKENS: In the 1970s, I was in Oxford with Richard Peto. I had the privilege to help him put together the APT Collaboration. We prespecified non-fatal MI, non-fatal stroke, and all vascular deaths as the combined endpoint. We specifically excluded silent MIs in the first cycle in '88 and the second with Rory Collins leading in '93, and the third with Colin Baigent, now called the ATT.

So, Merck, in my view, has used the correct APT now ATT definition. It is Novartis and the FDA that are at variance with what the APT definition.

I had a question for the FDA presenter. One of the things Peto told me is if you torture the data enough, they certainly will confess, but with that as a background, the lumiracoxib

comparison versus ibuprofen is 0.76, against naproxen it's 1.46, and the conclusion is that the drug is behaving differently in the two studies.

Well, the alternative hypothesis based on the evidence we have seen so far is that there may be a protective effect of naproxen and perhaps some harm of the shorter acting NSAIDs, a hypothesis supported by the basic science showing some deleterious actions of all the NSAIDs, but this potential beneficial effect on platelets of the longer acting NSAIDs.

So, I think it may not be necessarily true that we need to conclude that this drug is behaving differently in two studies with two very different comparators.

DR. VILLALBA: My conclusion was that I really don't know what to make of it, and that is why I need the opinion of other people here.

The conclusion really was that this probably a class effect, this is a very heterogeneous class, and you have all the degrees of selectivity there. So, that is what we need to

determine.

DR. WOOD: We have got Dr. Stephanie Crawford.

DR. CRAWFORD: Thank you. I would like to ask Dr. Sean Curtis to please come to the microphone if you are in the room.

Dr. Curtis, this morning you stated that in global markets, Merck is currently revising its labeling for etoricoxib to address new safety information relative to the safety of selective COX-2 inhibitors, so I am intrigued. In what manner, specifically, what is the sponsor stating in its revised labeling worldwide on the safety of this product?

DR. CURTIS: We participated in the European referral. It has been basically a referral process for all the COX-2 inhibitors, and that is actually just wrapping up, as you know. I, of course, have been here, but I am aware of now that there has now been wording for the label that talks--and this is basically class labeling in terms of contraindications--but I think really what

it boils down to, you know, we have been informed from the CHMP that there will now be a classwide contraindication for all coxibs related to congestive heart failure.

It was previously classed as 3 and 4, it has been extended to Classes 2 through 4. In addition, there will be contraindications in patients with established ischemic heart disease and/or cerebrovascular disease, so that will be class contraindication, class labeling.

In addition, for Arcoxia or etoricoxib, there will be contraindication in patients with hypertension whose blood pressure has not been adequately controlled.

So, that is obviously new information as of today, and that is, in essence, what I mean by working with the regulators, based on new and evolving information, to come up with product labeling that accurately and adequately reflects current knowledge.

DR. WOOD: I think she was asking you--which I suspect is going to be the committee's

focus the rest of the afternoon for both the sponsors, for the committee at least to decide what the committee would need to see before they approve new drugs like this--I think what Dr. Crawford was asking was what were the studies you were proposing to do to do that. Is that right, Dr. Crawford?

DR. CURTIS: Could you restate the question? I couldn't hear you.

DR. WOOD: I think the question was what studies were you proposing to do, that you thought would help get this drug approved in the future.

DR. CURTIS: As I reviewed through my presentation, we feel the underlying safety information that is most relevant to ensure that we are all comfortable with the safe and effective use of the drug, is to proceed with the studies that I outlined this morning, namely, EDGE II and MEDAL, which are, as I reviewed, opportunity to assess the long-term safety of the compound in contrast to traditional care, namely, diclofenac.

I reviewed the reasons why we chose diclofenac. There is pluses and minuses of the

comparators, but that is our primary method to further assess the compound at this point in time.

DR. WOOD: Put on slide 31 again, would you. That was the slide that showed the relative potency on the COX-1 and COX-2.

Basically, I think Dr. FitzGerald said earlier that he saw this as rofecoxib lite or something. So, given that you presumably wouldn't have expected to see a difference between your new drug and rofecoxib, it seems like you picked the next best thing to do as your comparator.

Naproxen is up there higher up, and you picked the one that was closest to rofecoxib to make your comparator, so the chances of seeing a difference seemed to me extraordinarily small, and I am not sure what that will teach us.

DR. CURTIS: Could we go to slide 1115, please. The slide that I just showed as part of the core presentation was the weighted mean average. I did also want to point out that diclofenac here, what is plotted here is again at steady state and a percent inhibition from baseline again of a COX-1

assay looking at platelet, thromboxane, B2.

This is a plot of inhibition both at peak and at trough of the exposure in the blood. You see diclofenac at trough has about 60 percent inhibition of thromboxane, but at peak, achieves levels that are close to 90 percent, so there is some variability in the degree of thromboxane inhibition throughout the dosing interval.

I went through the reasons why. I showed some clinical data, too, that did suggest that at least from a GI tract perspective, which, of course, is ultimately one of the key safety endpoints, that there is a way to differentiate diclofenac from other NSAIDs--excuse me--from what we consider COX-2 selective inhibitors.

I showed you data with valdecoxib and rofecoxib. In thinking about other comparator choices, there are limitations to the use of the other NSAIDs that I reviewed, and I think fundamentally one needs to keep in mind that diclofenac at this point is, in essence, probably the NSAID used most worldwide currently.

So, you know, in acknowledgment of the limitations of choosing any single individual comparator, and in acknowledging some of the

limitations that were reviewed perhaps in the TARGET study even, where if you do start to do sub-studies, you do run the risk of showing different estimates even with one comparator, even with the same compound.

We felt that doing a large study of the magnitude that I described for MEDAL against one comparator, and I reviewed the reasons why we chose diclofenac, was as reasonable a choice given all the alternatives.

DR. WOOD: Garret, are you still here? Maybe the question to him is supposing that study turns out with no difference, are you going to hear from him that he doesn't believe that tells you anything because it is just another COX-2 selective drug, is that what we are going to hear, Garret?

DR. FITZGERALD: I would take a slight different tack. We have heard the words "continuous variables" used quite a lot, and I

think it is a continuum from as one extreme, very selective, very long-lived drugs, going through shorter lived, less selective drugs through to very non-selective drugs.

I would guess that the ease of detection and the size of signal would move across that spectrum from being very large to being very small or undetectable.

So, I won't reiterate the reasons why. I think diclofenac resembles remarkably Celebrex with respect to selectivity, and I would view this trial as actually a very useful trial, beginning to address for us information that we need to know. I would cast it as a within COX-2 selective trial in that respect.

It is like we have a surrogate for Celebrex. We saw a lot of little trials with many flaws in the blood pressure arena yesterday, setting up Celebrex against rofecoxib with arguments about timing of dosing, and so on.

Well, here the rubber meets the road. We actually addressed the question of whether a

commonly used, relatively selective drug, diclofenac, stacks up in a way that segregates from a longer lived, much more selective drug, etoricoxib, so I think it does provide useful information in that regard, although I might cast the reasons for why I think it is useful in a slightly different way.

DR. WOOD: Any other questions? Dr. D'Agostino.

DR. D'AGOSTINO: This is both for Joel and Sean.

You raised the question, Sean, about doing a non-inferiority study, and I am wondering--that certainly will be a discussion that we will have--and I am wondering if you realized the implications of that.

When you look at, for example, slide 44, in your presentation, and you look at the EDGE study, was the EDGE study a non-inferiority trial?

DR. CURTIS: I actually wanted to clarify something that Dr. Schiffenbauer mentioned. So, the answer is no. The non-inferiority criteria

that I identified in the presentation is based on cardiovascular safety data accrued from three studies: EDGE, EDGE II, and MEDAL. So, the cardiovascular non-inferiority criteria is to be applied to the minimum 635 confirmed thrombotic events that will accrue from three studies.

DR. D'AGOSTINO: From the three studies, not one at a time.

DR. CURTIS: That's correct, but I am providing you data that is coming available, and EDGE had finished, and it is an important piece of information.

DR. D'AGOSTINO: That is comforting in terms of what is possible, but just to point out that on that result, that would not be very positive for you if you did the 1.3. You would actually, in that case, say that the comparator could be better. I mean that would be a conclusion in that study.

I don't want to go into the details of that, but one has to be very careful when they go the non-inferiority route, and we will talk about

that more. This slide frightened me a bit.

The other is if you do go the non-inferiority route, what about the inclusion of the aspirin individuals, it probably won't be a constant hazard in the sub-groups, but what will happen then with your non-inferiority. This was raised by Joel, and I would like an answer. I would love to hear what your answer is.

DR. CURTIS: Aspirin, of course, it is hard to win with that, and I will tell you why. On the one hand, you want to include patients with a range of baseline risk, and certainly one criticism of some of the studies is that patients with cardiovascular risk have not been included in these studies.

Both us and the FDA felt it was important, as the data provided to included patients with baseline cardiovascular risk, but, of course, those patients should be on aspirin.

So, we, of course, allow patients to be on aspirin as per clinical guidelines. As I mentioned, we expect about 30 percent of the total

patient cohort in the cardiovascular analysis will be on aspirin.

But I want to be clear, the primary analysis will be based on all patients whether they are on aspirin or not.

DR. D'AGOSTINO: But are you going to be assuming in the 1.3 that the hazard ratio will be the same within that sub-group, but just that it will be a different level of absolute risk? We will talk about those things, but those are serious implications.

I would have to have a study design where the very first thing you do is say, well, gee, I couldn't do what I set out to do, I have to look at subsets, namely, I have to get rid of the aspirin users because they are confounding things.

Was that the concern that the FDA is having?

DR. SCHIFFENBAUER: Yes, as I expressed, in the non-inferiority design where we don't have the placebo background, this would be a maneuver to make the two groups look more similar. I mean if

you extrapolate it to 60 percent or 80 percent aspirin use, I think the two groups would look almost identical, so you would end up having to look at subsets, that is true.

DR. WOOD: Dr. Abramson.

DR. ABRAMSON: Yes, I have a question for Dr. Villalba

DR. WOOD: Can we just deal with the first presentation first.

DR. ABRAMSON: I am sorry. Then, I will wait.

DR. WOOD: Dr. Gibofsky.

DR. GIBOFSKY: Dr. Curtis, I have a concern about the selective emphasis of data being presented in seeming replicate trials. If we go to slide 10, for example, and again in slide 46, you commented that etoricoxib was superior to naproxen in one of two pivotal studies, but similar in the other study, and based on that one study, you have used the term "superiority" at least twice in your presentation.

I guess I am kind of wondering, if you did

a back of the envelope calculation, like Dr. Fleming did yesterday afternoon when we were discussing two polyp trials, one of which we gave more focus to I think than the other, would you still be able to make this claim of superiority based on the meta-analysis with both trials?

DR. CURTIS: My point in highlighting the efficacy data was, of course, not to talk about a claim of superiority. The purpose was to provide data that provides you and all of us an opportunity to look at both the risks and the benefits of the compounds, and the data in RA were compelling, and I fully disclosed results from both studies.

Furthermore, the data, these really were the first studies that we are aware of that showed a statistically significant difference. So, my point was again in the context of an overall risk-benefit assessment, to claim--to not claim, but to show the data for this compound at the doses that were studied provide a level of efficacy that certainly should be part of the consideration.

I certainly would not be claiming any sort

of label claim or anything like that, because we are not here to talk about such things.

DR. GIBOFSKY: I take your point, but specifically, if you combine the second study with the first, would you use the word "superior" to naproxen, or would you use the word "equivalent" to naproxen?

DR. CURTIS: I can only talk about a clinical study within the context of that clinical study where patients were randomized evenly between treatment arms. I think it would be speculative to talk about combining the results.

DR. WOOD: Dr. Shafer.

DR. SHAFER: If you can go to slide 19, and we see here that once again the confidence bounds around the three groups do not really justify the breaking out of naproxen, it would appear to me, as a separate group.

Now, go to slide 44. Once again you have broken out naproxen as a separate group although it is not clear that the confidence bounds would support that either.

So, we have a pattern where you are constantly seeing a worse outcome compared to naproxen, and similar to rofecoxib, where the same

signal came up, you asked, I think, or you mean to imply to us that naproxen is intrinsically different, but we have heard multiple experts over the course of the last day and a half tell us that they don't believe that naproxen is intrinsically different.

We have seen observational trials in which there may be a modest effect of naproxen, but certainly nothing of the magnitude to explain a 1.5, 1.7 risk relative to naproxen that you have seen in your data, and even the sponsors themselves, Roche and Bayer, in their presentations, felt that naproxen did not have the cardio-protective effects that you have attributed to it.

So, first, I am disturbed that your primary analysis isn't versus NSAID comparisons, all NSAIDs, and then as a subgroup, you compare naproxen out. Instead, you pull naproxen out and

ask us, I mean the implication almost is that we should dismiss it, because it's naproxen, and then look at everything else. It concerns me that we aren't primarily looking at all NSAIDs as the comparison group.

Secondly, at this point in time, do you truly believe that naproxen and the postulated cardio-protective benefits of naproxen truly explain the difference that you are seeing, and that we are not actually seeing a very solid signal for intrinsic increased cardiovascular toxicity with the COX-2 antagonists?

DR. WOOD: And while you are answering that question, tell us why the right study wouldn't be to do a naproxen with omeprazole versus your drug. I mean you obviously believe naproxen beats the drug, right? And the only advantage of the drug over naproxen is a GI benefit.

Supposing omeprazole gave you the GI benefit and you still had the cardiovascular benefit, wouldn't that be the optimal therapy? And why, given your data here, did you choose to go

with the drug that has less benefit than naproxen? I still don't understand that.

DR. CURTIS: I am going to answer your second question first. Naproxen clearly is a very effective drug, however, as we heard repeatedly today, patients have different responses to therapies. Again, the reason people with arthritis take drugs is so they can have some relief. Not everybody responds to naproxen.

So, I think naproxen clearly is a very logical choice for many patients, but there are going to be patients who do not respond to naproxen, and when you factor in GI risk, adding a PPI certainly would appear to likely to mitigate some of the risk, but you are still going to be left with patients who don't respond to naproxen, who still are going to have a residual GI risk, and we have seen data that suggests even when you add a coxib or a PPI to an NSAID, there is still room to improve from a GI safety perspective.

So, I think that as a therapeutic option, selective COX-2 inhibitors, including etoricoxib,

still have a role. As to why we chose not to use naproxen as the comparator in our outcome study, I reviewed the reasons. We have now seen qualitative differences in cardiovascular outcomes against naproxen with three different COX-2 selective inhibitors: rofecoxib, etoricoxib, and lumiracoxib.

We felt that doing an outcome study against naproxen, we would likely replicate that observation again. We felt it was important to accrue additional data against another traditional NSAID that was used widely around the world to get a more firm estimate of what the cardiovascular risk looked like against another NSAID.

DR. WOOD: You looked at that data. You saw that naproxen beats your drug. So, you decided to pick one that didn't look like it would--because it is as selective as your drug is--and you are going to come back with that data and say wow, it doesn't produce any cardiovascular signal because it's the same as diclofenac. That doesn't make any sense.

DR. CURTIS: Again, I think it is important to remember that the qualitative differences that were observed against naproxen

were being seen at the same time that no differences were being observed with non-naproxen NSAIDs, and in a time frame like a year for which a difference from placebo with COX-2 inhibitors has not been appreciated.

So, I think all that data, to me, continues to say that there is something different about naproxen. I can't quantify that, I don't think the data allow that, but there clearly appears to be something different about comparisons to naproxen to the other NSAIDs.

DR. WOOD: I understand that, but the issue that has changed since hour initial studies with naproxen is that we now have three randomized trials against placebo in which placebo beat the drug. So, using an active comparator that you have chosen to match in terms of cardiovascular adverse events, etoricoxib, isn't acceptable in terms of showing that the drug doesn't have an effect on

cardiovascular mortality or morbidity.

It might have been acceptable in the days when you believed that naproxen was beneficial and that that was the total explanation, but by your own admission, you don't believe that anymore.

DR. CURTIS: So, if I understand the question, you are asking why we are not doing a large outcome study against naproxen?

DR. WOOD: I guess I am asking you what you are going to learn from the diclofenac study. You are certainly not going to be able to say that this drug does not produce cardiovascular problems given that you have deliberately chosen a drug that looks as similar to etoricoxib as you can get, and from your earlier studies, namely, this one, you have seen that it does produce a difference with naproxen, and it doesn't appear to produce a difference with this, and it has got a very similar pharmacology.

So, if you can imagine an imputed placebo arm here, and given what we know about placebo, you would predict that this drug would do worse than

placebo, and you won't be able to exclude that from the study you are designing.

DR. CURTIS: The data that are emerging, that we have all seen the APPROVe data, we have all seen the difference against celecoxib in the APC study, to us, that suggests a class effect. I have showed you our placebo-controlled data for etoricoxib, it's very limited.

With that being said, the class effect related to COX-2 inhibition, we would presume extends to etoricoxib, and, to us, the real clinical question is in patients who require chronic treatment, what is the cardiovascular safety against a standard of care, and for the reasons I reviewed, we chose diclofenac.

DR. WOOD: So, let me be sure I understand. So, we are going into this study saying that we know and believe that the drug will produce a cardiovascular signal, we are just trying to work out if it's better or worse than diclofenac.

DR. CURTIS: No, I think what we are

asking is--

DR. WOOD: Well, that is what you just said, isn't it?

DR. CURTIS: If I could rephrase what I said, I think what we are saying is we are suggesting there is a class effect, and we are not sure how big the class is, and we feel that the MEDAL study will help provide information to address that specific question, whether cardiovascular safety for selective COX-2 inhibitor is the same or different than that of a traditional NSAID, one that is the most widely used NSAID around the world currently.

DR. WOOD: Okay. Dr. Bathon.

DR. BATHON: I was going to say much the same thing. I have the same concerns about this especially since naproxen is the most widely prescribed NSAID in the U.S. and the most relevant to our practice, whereas, diclofenac has much more hepatotoxicity especially in RA patients where methotrexate is co-administered.

So, I think it would have added a lot more

to our clinical practice management to see another big trial against naproxen rather than diclofenac, plus you could have added these results to your prior trials and had more power to assess the effect of naproxen versus etoricoxib with all of your trials combined, but now, since you are using diclofenac, you don't have that extra power.

DR. WOOD: Dr. Reicin.

DR. REICIN: Let me just make one comment, and as all you start to talk about designing clinical trials, I think you will see, as many of you know, it is quite difficult and you cannot answer every question in every study.

MEDAL was started over two years ago, and at that time there was no placebo-controlled data to suggest that COX-2 inhibitor was different than placebo. Obviously, that has changed. The studies are fully enrolled and ongoing.

I can't disagree with you that the idea of doing a naproxen plus PPI study versus a COX-2 inhibitor isn't a good idea and isn't an important question. Unfortunately, we didn't design that

study, we designed this one, and I think, as Garret said, it will provide information about how big the class is.

While some of you may not be using diclofenac, it is the most widely used NSAID in the world, and therefore, I think it will provide beneficial safety data to see what a selective COX-2 inhibitor looks like versus a non-selective inhibitor albeit not as non-selective as naproxen.

DR. WOOD: Thanks.

Dr. Dworkin.

DR. DWORKIN: Yes, a simple question. You said that the CPMP had come up with class labeling, but you neglected to tell us CPMP defined the class. Is it all NSAIDs, is it COX-2 inhibitors, and if the latter, what drugs were included in that subclass?

DR. CURTIS: I am going to give my understanding as a clinician who has been here for the last 48 hours, but my understanding it is specific to what we consider the selective COX-2 inhibitors - celecoxib and etoricoxib, and that

that is how the class is being defined currently.

DR. DWORKIN: So, those two drugs, but not, for example, Meloxicam.

DR. CURTIS: Dr. Erb, would you like to comment on any additional agents?

DR. ERB: Yes, Dennis Erb from Regulatory Affairs.

The CHMP is included in the class, what we have been referring to today as the coxibs, lumiracoxib, celecoxib, and etoricoxib, and valdecoxib.

DR. WOOD: Dr. Platt.

DR. PLATT: More on the history of the choice of comparators. Dr. Schiffenbauer, could you tell us more about the conversations between the agency and the sponsor around the choice of comparators?

Your comments and the materials you presented to us suggested that you had reservations about that choice.

DR. SCHIFFENBAUER: Yes, we had extensive discussions with the sponsor. At the time we

appreciated the difficulties doing a placebo-controlled trial, but we had requested--and I can't quote you whether it was additional comparators or comparator--but we had recommended strongly that additional agents be studied to get a better handle on the true cardiovascular risk.

DR. PLATT: Was there discussion about naproxen as a comparator?

DR. SCHIFFENBAUER: Not specifically other than to mention that we recommended additional comparators.

DR. WOOD: Dr. Farrar.

DR. FARRAR: One of the things that strikes me about all of the studies that we have been looking at, and perhaps most in the comparison of studies that we are still waiting for some data on, namely, APC and CPAC, is the difference in the underlying risks between some of these different comparisons.

I noticed that in your particular study, the cardiovascular risk, you felt that 38 percent--I think that was the number--that in your

slide you had 38 percent at an increased risk of cardiovascular disease with 24 percent on aspirin and 10 percent of them as being diabetic.

I just wondered if you could comment on what the mix of the MEDAL study is likely to be or is. I mean you certainly would have the data at this point.

DR. CURTIS: Yes. 1103, please. The MEDAL study population is, as I mentioned, both OA and RA patients, so approximately 75 percent of the patients have OA and about a quarter have RA. What is represented here are the risk factors for the cohort, the entire cohort, and it is not dissimilar to what I highlighted for the EDGE study.

These are basically baseline medical diagnoses at the time of entry into the study, so about half have hypertension, which is a little higher than the EDGE study, which was about 40 percent, as you see here, the individual cardiac risk factors, and this 12 percent of history, that is documented atherosclerotic cardiovascular disease. The 38 percent that I quoted for the EDGE

study was patients with this or to primary risk factors.

So, that percentage, if I were to calculate that percentage for this study, it would probably be a little higher than EDGE, probably about 40, 42 percent. So, these are the patients in MEDAL.

DR. FARRAR: If I could just follow up and ask actually Garret FitzGerald, whether he has any comments on the relative risk of patients who have either high or low cardiovascular risk factors.

I mean we know from the study, the CABG study, that patients with very high risk clearly have a marked increased response to these drugs, and whether people who have cardiac risk factors are also in that category, or whether it really is restricted to sort of the release of active agents from the surgical procedure.

DR. FITZGERALD: Well, obviously, the actual information we have relevant to your very important question is conjecture. What we know mechanistically is that what we would expect would

be the response to thrombogenic stimuli would be enhanced, as would the predisposition to the other cardiovascular adverse manifestations of this mechanism, namely, hypertension and atherogenesis.

So, for example, if a population was enriched in patients with secondary hyperaldosteronism, they would be more prone, on average, to exhibit hypertension in response to an NSAID or particularly a selective COX-2 inhibitor.

Similarly, if they were at advanced risk of hemostatic activation, they would be prone to the thrombogenic complications, and I think with the CABG patients, we had an extreme phenotype of excessive hemostatic activation.

Now, as we move away from that extreme through what we call "heightened" cardiovascular risk, there is probably a continuum of predisposition that is a mix of predisposition to the various types of manifestation of this mechanism that could occur.

So, we have only crude indicators obviously, and to some extent, as I talked about

yesterday, it's in the eye of the beholder as to what defines heightened cardiovascular risk, but on average, the group defined as having higher cardiovascular risk, for example, RA compared to OA, on average would be expected to show a signal easier than in a group with low cardiovascular risk.

I mean I would think with this type of study, we may have had a premonition of the outcome from the EDGE result. For example, if we think of these two drugs as defining the limits of a class, just for fun, one could say like in the EDGE results, you wouldn't see a distinction in the hard GI endpoints or the hard cardiovascular endpoints, but what you might see a distinction in is their fringe surrogates, which might be easier to pick up, such as discontinuations because of hypertension or discontinuations because of GI side effects, and that is actually what was seen at the two ends of the spectrum in the EDGE result.

DR. WOOD: But we do know from the APPROVe study that the point estimate, even in the people

with no history of cardiovascular disease, which would be the only clinical measure we could reasonably use to distinguish that, it is still substantially greater than 1.

DR. FITZGERALD: Yes, I mean I did try to raise the issue yesterday that how we define underlying clinical substrate is an inexact science, on the one hand, and on the other, that many other factors that we discussed yesterday could play into the likelihood of manifestation of risk at the individual level.

DR. WOOD: Steve.

DR. NISSEN: I want to maybe bring us back to earth a minute and talk about the time horizon for such a trial. I feel compelled to point out that we have got a lot of history in cardiovascular medicine of studying drugs for atheroprotective effects.

Those trials are typically not one year or two years or even three years, they are typically five-year studies, and in many of them, let's take a blockbuster class of drugs like the statins.

Look at the CARE trial. The CARE trial, the Kaplan-Meier curves didn't diverge at all for two years, and so now we have got a drug here that

may be promoting atherogenesis, and so we are going to say, well, we are going to have a 20-month mean exposure, and if it doesn't produce a problem, then, there must not be a problem, and I am not sure that's right.

The problem we have is that what has been done here is the sample size has been increased to a large sample size in order to shorten the duration, but that may not be the same as studying a more modest size group of patient for three or four years.

It is assuming that the hazard is constant over time, and I am not so sure that it is here. If, in fact, Garret is right, and he has been right about a lot of things, that these drugs are potentially atherogenic, then, an atherogenic intervention may not produce an effect for several years.

So, how can you reassure us here that a

20-month mean exposure is enough to allow us to move forward with a drug like this?

DR. CURTIS: I think what you are touching on is--I am not going to disagree--what I am going to point out is the fact that I think running an arthritis study is perhaps different, and I have not designed outcome studies, cardiovascular, other than this--but to keep arthritis patients in studies is difficult, and that has to do with the treatment of the disease.

As the rheumatologists here can speak to, a traditional trial has 40 percent of the patients discontinuing after one year, and another 10 to 20 percent dropout rate every year subsequent, so there are significant practical limitations to keeping patients on study therapy into the time frame that you proposed, Dr. Nissen.

So, that is a practical limitation to running arthritis studies.

DR. NISSEN: I just would also point, however, that the patients that we studied initially with these atheroprotective drugs were

very high risk secondary prevention patients. These were not low risk people.

So, you are going to take a lower risk population and you are going to look for a signal at a 20-month mean duration, and that signal may actually take longer to show up in a lower risk population.

So, I am troubled by how long we have to look for with a drug like this before we really can say there isn't a problem. People may take these drugs for a decade. We heard that from people at the microphone here.

So, these are some of the things that trouble me about the whole question.

DR. WOOD: I have got a whole list of questions here, but I want to keep us moving here.

So, are there any people who have burning questions that they want to torture Dr. Curtis with before we let him off? It has to be specific. We will take Tom, we have not heard from you yet.

DR. FLEMING: Burning?

DR. WOOD: Burning.

DR. FLEMING: There are two or three issues I want to quickly review. You didn't mention in EDGE the new ischemic heart disease or

the heart failure, pulmonary edema, cardiac failure. I think the FDA indicated in their review, there was a 25-19, and a 14-6, so basically about a 30 percent relative increase and a doubling in those two, is that your understanding?

DR. CURTIS: The numbers, yes, Dr. Schiffenbauer quoted, those are the correct results, and that information was in your background package.

DR. FLEMING: And then very quickly, your slide 19 and then your slide 25. On your slide 19, do you have the analogous slide for the APTC results? If you don't, my understanding is the relative risks are less favorable than this or more unfavorable, depending on your perspective.

They are 1.8, 0.87, and 2.72?

DR. CURTIS: That is correct, yes.

DR. FLEMING: So, essentially, we are looking at with roughly a 3 to 2 randomization in

the aggregate, and the aggregation of these events here, we are looking at 43 versus 12, so a pretty substantial excess in the critical APTC measures.

DR. CURTIS: Well, again, as you know, the APT events in total are smaller than these numbers, so your confidence intervals around those point estimates are, in fact, much broader.

DR. FLEMING: But at 43 to 12, they are certainly well outside of unity.

The last thing is slide 25. You give the mortality results, but it is difficult to really see in this scale, but it appears that the relative risks are roughly in the range of 1.6 against placebo, also 1.6 against naproxen, and 1.2, and then in addition to that, it is also 1.33 in the EDGE trial.

So, it looks as though when you look in terms of relative risks, that you are looking at about a 1.5 relative risk on mortality across the aggregate of these data.

DR. CURTIS: Yes, this slide shows the rate with the confidence interval. I don't have

the relative risk.

DR. FLEMING: But those aren't relative rates is my point.

DR. CURTIS: That's correct, these are absolute rates here.

DR. WOOD: So, you are saying this stuff doesn't look it's good for you. Anyone else who has a burning question? Go ahead.

MS. MALONE: It's burning. I would like a simple answer. How much different--now, I heard him call this like Vioxx lite, I believe I heard him say that--how different is this from Vioxx, you know, chemically, and do you see it as a substitute for people who are perhaps taking Vioxx?

DR. WOOD: I think we are talking about diclofenac. It was the comparison to diclofenac which had been referred to.

MS. MALONE: He also did a presentation on etoricoxib. So, can he answer that?

DR. WOOD: You are asking me?

MS. MALONE: No, him. Okay, I am sorry, I thought you had said that about etoricoxib.

DR. CURTIS: Can you clarify the question, please?

MS. MALONE: I am just wondering how the

compound in etoricoxib compares to Vioxx.

DR. WOOD: You mean chemically?

MS. MALONE: Yes, but in simple terms.

DR. CURTIS: The human whole blood assay, if that is your specific question, the human whole blood, which is sort of the gold standard, that shows a degree of COX-2 selectivity that is greater for this drug, but in the clinical dose range, etoricoxib, just like rofecoxib, just celecoxib, just valdecoxib, are selective for the COX-2 enzyme in the clinical dose range, so in that regard, they are similar.

Does that answer your specific question?

MS. MALONE: I am just wondering, you know, I have heard people say that Celebrex or Vioxx was much more selective than Celebrex and Bextra, and where does this fit in, in that scheme?

DR. CURTIS: Again using the human whole blood biochemical assay, this drug would be

considered more selective, but I think the key concept, at least for me as a clinician, is that in the dose range that these drugs are used, they all selectively inhibit the COX-2 enzyme and do not inhibit COX-1.

DR. WOOD: Let's move on to the next set of presenters and let Dr. Curtis off the hook. Thank you very much.

Are there questions for the Novartis presenters from the committee? Some of the people who are still waiting for the questions, we will begin with them if they want to start with the other ones. Dr. Abramson had one, I know, and we punted.

DR. ABRAMSON: That was the TARGET presentation by Dr. Villalba. I would like to just throw slide 9 up, if we could, and follow up on a point that Dr. Hennekens made when we started this session.

In that slide, you combined the two component studies of TARGET and again said that lumiracoxib behaved differently in the two studies,

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.

Proposed NSAID Package Insert Labeling Template1 (Revised XXX/05)

TRADENAME (Established name which should always include dosage form) Strength

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. 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**).

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

Gastrointestinal Risk

- NSAIDs 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- No change

CLINICAL PHARMACOLOGY- No change

INDICATIONS AND USAGE

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

TRADENAME is indicated:

* For reduction of fever [in patients age]
* For relief of mild to moderate pain [in patients age]
* For relief of signs and symptoms of juvenile arthritis.
* For relief of the signs and symptoms of rheumatoid arthritis
* For relief of the signs and symptoms of osteoarthritis.
* For treatment of primary dysmenorrhea.
* For acute or long-term use in the relief of signs and symptoms of the following:
    1. Ankylosing spondylitis
    2. Acute painful shoulder (Acute subacromial bursitis/supraspinatus tendinitis)
    3. Acute gouty arthritis

Put in the product specific indication(s)

1 Throughout this package insert, the term NSAID refers to a non-aspirin non-steroidal anti-inflammatory drug.

CONTRAINDICATIONS

TRADENAME is contraindicated in patients with known hypersensitivity to GENERIC NAME.

TRADENAME 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**).

TRADENAME 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

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. 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 an NSAID, 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 events 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 an NSAID does increase the risk of serious GI events (see **GI WARNINGS**).

Two large, controlled, clinical trials of a 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

NSAIDs, including TRADENAME, can lead to 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 TRADENAME, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. TRADENAME should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects- Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including TRADENAME, can cause serious gastrointestinal (GI) adverse events including inflammation, 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. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, 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 those 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 for 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 in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. 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 a nonsteroidal anti-inflammatory drug 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.

Advanced Renal Disease

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

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to TRADENAME. TRADENAME 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

NSAIDs, including TRADENAME, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. 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, as with other NSAIDs, TRADENAME should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General
TRADENAME cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.
The pharmacological activity of TRADENAME in reducing [fever and] inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.
Hepatic Effects
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including TRADENAME. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.
A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with TRADENAME. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), TRADENAME should be discontinued.
Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs, including TRADENAME. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including TRADENAME, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.
NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving TRADENAME who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.
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, TRADENAME 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 an

NSAID 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. TRADENAME, 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 when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Cardiovascular Effects**).

2. TRADENAME, like other NSAIDs, can cause GI discomfort and, rarely, serious GI 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 observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Gastrointestinal Effects: Risk of Ulceration, Bleeding, and Perforation**).

3. TRADENAME, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. 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 should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

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). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

6. Patients should be informed of the signs of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see **WARNINGS).**

7. In late pregnancy, as with other NSAIDs, TRADENAME should be avoided because it will cause premature closure of the ductus arteriosus.

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 their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash,

etc.) or if abnormal liver tests persist or worsen, TRADENAME should be discontinued.

Drug Interactions

ACE-inhibitors

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

Aspirin

[When TRADENAME in administered with aspirin, its protein binding is reduced, although the clearance of free TRADENAME is not altered. The clinical significance of this interaction is not known; however,] as with other NSAIDs, concomitant administration of GENERIC NAME and aspirin is not generally recommended because of the potential of increased adverse effects.

Furosemide

Clinical studies, as well as post marketing observations, have shown that TRADENAME can reduce the natriuretic effect-of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see **PRECAUTIONS, Renal Effects**), as well as to assure diuretic efficacy.

Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Drug/Laboratory Test Interactions

Only if positive interactions have been observed. (See 201.57 (f)(4)(N).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Usually only if significant findings have been observed. (See 201.57 (f)(5))

Pregnancy

Teratogenic Effects. Pregnancy Category C.

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Nonteratogenic Effects

Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and Delivery

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of

TRADENAME on labor and delivery in pregnant women are unknown.

Nursing Mothers

It is not known whether this drug is 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 TRADENAME, 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 ??? [have, have not] been established.

Geriatric Use

As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

ADVERSE REACTIONS- No change

OVERDOSAGE- No change

DOSAGE AND ADMINISTRATION

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

After observing the response to initial therapy with TRADENAME, the dose and frequency should be adjusted to suit an individual patient's needs.

For the relief of ????, the recommended dose is ??? mg given orally ?? times per day.

[Different dose strengths and formulations (i.e., capsules, tablets, suspensions) of the drug are not necessarily bioequivalent. This difference should be taken into consideration when changing {formulation (type, strength)}.]

HOW SUPPLIED- No change

Medication Guide
for
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG).

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines are use to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:

- different types of arthritis
- menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:

- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breastfeeding. **NSAID medicines may harm your baby.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:	**Other side effects include:**
• heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma	• stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting • dizziness

Get emergency help right away if you have any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- skin rash or blisters with fever
  unusual weight gain
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.

- Some of these NSAID medicines are sold in lower doses without a prescription (over –the –counter). Talk to your healthcare provider before using over –the –counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	**Tradename**
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbirofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

1. * Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke."

This Medication Guide has been approved by the U.S. Food and Drug Administration.

FDA Reviews of Current Submission—

Expanded Executive Summary from Clinical Review

EFFICACY

The applicant has provided adequate evidence of efficacy for etoricoxib, 30 mg and 60 mg, for the relief of signs and symptoms of osteoarthritis. This conclusion is based upon a total of seven studies.

- Four adequate and well-controlled studies demonstrated the efficacy of 30 mg of etoricoxib in treating osteoarthritis for 12 weeks.
- Two adequate and well-controlled studies demonstrated the efficacy of 60 mg of etoricoxib in treating osteoarthritis for 12 weeks.
- One large Phase 2 dose-ranging study showed evidence of dose-response between daily doses of etoricoxib ranging from 5 mg through 60 mg.

SAFETY

To evaluate the safety of etoricoxib, the applicant conducted an extensive clinical development program and has submitted a safety database consisting of nearly 42,000 subjects, approximately half of whom received etoricoxib, for as long as 42 months.

The safety program consisted of the MEDAL Program, comprised of three component studies: MEDAL, EDGE and EDGE II. These were large outcome studies that enrolled patients with osteoarthritis (OA) or rheumatoid arthritis (RA) randomized to either 60 mg or 90 mg of etoricoxib per day versus an active comparator, diclofenac 150 mg per day. These studies were designed to collect data on outcomes of interest, particularly those involving the cardiovascular (CV), gastrointestinal (GI), and renovascular (RV) organ systems. These studies had substantial follow up (mean duration of therapy was 20, 19, and 9 months for MEDAL, EDGE II, and EDGE, respectively).

To complement the MEDAL Program, the applicant analyzed and submitted data from 18 Phase 2 and 3 studies. These studies were heterogeneous in that they enrolled a diverse patient population (OA, RA, chronic low back pain, ankylosing spondylitis) and employed placebo controls and active controls including diclofenac, naproxen, celecoxib, and ibuprofen. These studies were of four to 52 weeks duration.

The key safety findings are:

1. **Cardiovascular risk**

   The risk for thromboembolic cardiovascular events was comparable for etoricoxib and diclofenac. The CV events from the MEDAL Program were adjudicated by a blinded "Vascular Event" committee whereby the event was categorized, e.g given a diagnosis such as "acute myocardial infarction," and classified as confirmed or unconfirmed. These data were subjected to a statistical analysis comparing the etoricoxib treatment group and the diclofenac treatment group using non-inferiority hypothesis testing.

Table 1 shows the summary statistics for the entire MEDAL Program using the Antiplatelet Trialists' Collaboration (APTC) definition of cardiovascular event for confirmed events. The data show that etoricoxib and diclofenac had essentially overlapping point estimates and confidence intervals.

Table 1 Summary statistics for CV outcomes, pooled MEDAL Program

Absolute Rate and Relative Risk (and Associated 95% CI)
Confirmed APTC Combined Endpoint
Pooled MEDAL Program
(Per-Protocol, mITT, and ITT Approaches)

Analytical Approach	Treatment	N	n / PYR[†]	Rate[‡] (95% CI)	Relative Risk (95% CI)
Primary Analysis					
Per-Protocol Approach	Etoricoxib	16819	216 / 25851	0.84 (0.73 , 0.95)	0.96 (0.79 , 1.16)
	Diclofenac	16483	216 / 24787	0.87 (0.76 , 1.00)	
Secondary Analysis					
Within 14 Days (mITT) [§]	Etoricoxib	17412	231 / 26402	0.87 (0.77 , 1.00)	0.96 (0.80 , 1.15)
	Diclofenac	17289	232 / 25416	0.91 (0.80 , 1.04)	
Sensitivity Analyses					
Within 28 Days (mITT) [§]	Etoricoxib	17412	237 / 27059	0.88 (0.77 , 0.99)	0.95 (0.80 , 1.14)
	Diclofenac	17289	239 / 26068	0.92 (0.80 , 1.04)	
All Events (ITT)	Etoricoxib	17412	332 / 39894	0.83 (0.75 , 0.93)	1.02 (0.87 , 1.18)
	Diclofenac	17289	325 / 39623	0.82 (0.73 , 0.91)	

[†] Patient-years at risk.
[‡] Number of events per 100 patient-years
[§] Events between trial Start date and within *specified* days after study therapy discontinuation
N=total number of patients, n=the number of patients with events; APTC=Antiplatelet Trialists' Collaboration; CI=confidence interval; mITT=modified intention-to-treat; ITT=intention to treat.

In contrast, the data for cardiovascular risk from the smaller and shorter non-MEDAL studies are dependent on the comparator. Etoricoxib appears to have less CV risk compared to non-naproxen NSAIDs, greater risk compared to naproxen, and greater risk compared to placebo, but the overall number of events and duration of exposure were much smaller than for the MEDAL studies.

2. Gastrointestinal safety and tolerability

Similar to the process used for CV events, for the MEDAL Program, a GI event committee categorized all GI events and classified them as confirmed or unconfirmed. In addition, the GI adjudication procedure further classified events as complicated or not complicated. Complicated events were defined as highly significant medical events such as intestinal perforation or obstruction, ulcers associated with a significant GI hemorrhage such as those requiring transfusion or resulting in orthostatic changes in blood pressure. These results are displayed in Table 2. The rate of medically significant, confirmed/complicated events was approximately the same for both treatment groups. Inclusion of not complicated events increased the rate more for the diclofenac group than the etoricoxib group. Similarly, inclusion of unconfirmed events increases the rate of events for

diclofenac more than etoricoxib, but there is no rationale for including these when there was a prespecified adjudication committee.

Table 2 Upper GI outcomes, pooled MEDAL Program

	Etoricoxib		**Diclofenac**	
Event Classification	**N (%)**	**Rate* (95% CI)**	**N (%)**	**Rate* (95% CI)**
Confirmed/complicated	78 (0.45)	0.30 (0.23,0.37)	82 (0.47)	0.32 (0.26,0.40)
Confirmed/complicated and not complicated	**176 (1.01)**	**0.67 (0.57,0.77)**	**246 (1.42)**	**0.97 (0.85,1.10)**
Confirmed and unconfirmed/ complicated	103 (0.59)	0.39 (0.32,0.47)	123 (0.71)	0.48 (0.40,0.58)
Confirmed and unconfirmed, complicated and not complicated	201 (1.15)	0.76 (0.66,0.87)	282 (1.63)	1.11 (0.99,1.25)

*Events per 100 patient-years

To further evaluate the difference in event rates between the confirmed/ complicated events and the confirmed/complicated and not complicated events, the individual events were examined as demonstrated in Table 3. The table shows that the favorable results for etoricoxib over diclofenac are based almost completely on the number of uncomplicated ulcers.

Table 3 Specific upper GI events by confirmed/complicated or confirmed/complicated and not complicated

	Etoricoxib		Diclofenac	
Category	# events C/C	# events C/C&NC	# events C/C	# events C/C&NC
Ulceration	38	175	32	249
Perforation	5	5	11	11
Obstruction	2	2	2	2
Hemorrhage	70	78	71	76

Analyses of GI tolerability were based on discontinuation rates for GI-related clinical (dyspepsia, nausea, etc.) and laboratory (otherwise unexplained decrease in hemoglobin) adverse events (AEs), and favored etoricoxib over diclofenac.

Both aspirin (ASA) and gastroprotective agents (GPA) such as proton pump inhibitors, H_2-blockers, misoprostol, and antacids, were permitted and widely used. An analysis of the use of ASA and GPAs by drug class and dose was conducted and the use of these products was matched across treatment groups, so these products are not responsible for the differences found.

From the non-MEDAL (conventional Phase 2 & 3) database, it was possible to compare etoricoxib to other NSAIDS, specifically naproxen, ibuprofen, and celecoxib. However, for many of these studies, there were very few events in any one treatment arm, making it difficult to form reliable conclusions.

The analysis of lower GI events (perforations, obstructions, and bleeds) was actually the prespecified primary GI safety outcome for the MEDAL Program. The results of the analyses showed a numerical but not statistical superiority for

etoricoxib, regardless of whether the event was complicated or not. Table 4, following, summarizes the lower GI event rates.

Table 4 Lower GI outcomes, pooled MEDAL Program

	Etoricoxib		**Diclofenac**	
Event Classification	**N (%)**	**Rate* (95% CI)**	**N (%)**	**Rate* (95% CI)**
[Confirmed/ complicated]	77 (0.44)	0.29 (0.23,0.36)	87 (0.50)	0.34 (0.27,0.42)
[Confirmed/ complicated and not complicated]	84 (0.48)	0.32 (0.25,0.39)	96 (0.56)	0.28 (0.31,0.46)

*Events per 100 patient-years

3. Renovascular safety

Unlike the CV, GI, and hepatic events, the applicant did not prespecify a pooled analysis of renovascular (RV) events across the three studies, postulating that they would be sufficiently numerous not to require the additional power of pooling, but did pooled analyses anyway. The applicant investigated the following four aspects of RV safety.

a. Effects on blood pressure - Hypertension (HTN) was evaluated by the incidence of discontinuation for HTN, mean changes in blood pressure from baseline, HTN-related adverse events (of lesser severity than those that required discontinuation), and prespecified criteria for increases in blood pressure.

   Table 5 shows the summary statistics for the rates of discontinuations for hypertension-related events in the pooled MEDAL Program. The table shows that, for each dose, study and population, etoricoxib was associated with a significantly higher rate of discontinuations.

Table 5 Discontinuations for HTN-related events, MEDAL Program

Analysis of Prespecified Adverse Experiences - Discontinuations Due to Hypertension-Related Adverse Experiences by Disease and Dose
MEDAL Study (OA/RA), EDGE II (RA), EDGE (OA)
MEDAL Study OA Cohorts Presented Separately

	Osteoarthritis						Rheumatoid Arthritis		
	60 mg vs. Diclofenac			90 mg vs. Diclofenac					
	Etoricoxib 60 mg	Diclofenac 150 mg	Difference in Proportions (95% CI)	Etoricoxib 90 mg	Diclofenac 150 mg	Difference in Proportions (95% CI)	Etoricoxib 90 mg	Diclofenac 150 mg	Difference in Proportions (95% CI)
Study	n/N (%)	n/N (%)	Etoricoxib 60 mg - Diclofenac	n/N (%)	n/N (%)	Etoricoxib 90 mg - Diclofenac	n/N (%)	n/N (%)	Etoricoxib 90 mg - Diclofenac
MEDAL (OA)	146/6769 (2.16)	109/6700 (1.63)	0.53 (0.07, 1.00) p = 0.027	55/2171 (2.53)	24/2162 (1.11)	1.42 (0.63, 2.26) p < 0.001			
MEDAL (RA)							69/2841 (2.43)	46/2855 (1.61)	0.82 (0.08, 1.57) p = 0.030
EDGE II (RA)							51/2032 (2.5)	31/2054 (1.5)	1.00 (0.14, 1.89) p = 0.025
EDGE (OA)				81/3593 (2.3)	23/3518 (0.7)	1.60 (1.06, 2.18) p < 0.001			

n/N=Number of patients discontinuing for adverse experience/number of patients treated; CI=Confidence Interval
Boxes shaded in gray indicate no applicable data. Includes adverse experiences up to and including the 14 day post therapy discontinuation.
Although a patient may have had two or more adverse experiences, the patient is counted only once in the overall category. The same patient may appear in different categories. The 95% confidence interval (CI) is calculated by Wilson's Score Method. P-value is from Fischer's exact test.
[Ref. 5.3.5.1: P061, P066, P072]

For all other analyses evaluating hypertension (i.e. mean changes from baseline), etoricoxib was consistently worse than diclofenac.

b. Development of Congestive Heart Failure (CHF) – CHF was handled similarly to the CV and GI events with an adjudication committee. Data analyzed included discontinuations and serious adverse events for CHF in the MEDAL Study, adverse events classified as CHF (EDGE and EDGE II), and CHF cases that resulted in hospitalization for the entire MEDAL Program. The findings favor diclofenac over etoricoxib although none of the differences reached statistical significance.

c. Development of edema – Data for edema-related events that required discontinuation and edema-related AEs of any severity were assessed. Similar to the other RV evaluations, etoricoxib tended to be inferior to diclofenac.

d. Development of renal-related laboratory abnormalities – Renal-related lab abnormalities were evaluated by discontinuation for such events, mean changes in serum creatinine and development of prespecified increases in creatinine. Except for one etoricoxib subgroup at 90 mg, diclofenac and etoricoxib appeared similar with regard to abnormalities in creatinine and BUN.

RV events - Non-MEDAL database

The applicant's analysis of the non-MEDAL data provided some information about the 30 mg dose of etoricoxib and active comparators other than diclofenac.

There were too few events in some categories, particularly discontinuations due to edema-related AEs or HTN-related AEs and AEs realated to CHF, to make meaningful comparisons. For hypertension-related AEs and edema-related AEs, all of the NSAIDs were numerically worse than placebo. Numerically, ibuprofen was comparable to the highest etoricoxib dose (120 mg) for HTN. For edema-related AEs, there were no notable differences across the NSAIDs. There was also a dose response across the four etoricoxib groups for hypertension-related AEs.

4. The common adverse events for etoricoxib are typical for an NSAID.

Common adverse events were collected in the non-MEDAL database. These included AEs such as abdominal pain, dyspepsia, diarrhea, nausea, hypertension, edema, dizziness, nasopharyngitis, upper respiratory infection, and headache at incidences typical for an NSAID. These adverse events are typical for this class of drug and patient population. There were no signals for any unusual or rare adverse events.

5. Lower rates of elevations in transaminases.

The applicant evaluated hepatic safety by evaluating three measures: discontinuations for hepatic adverse experiences, mean change from baseline in serum transaminase levels, and prespecified criteria for elevations in transaminases (i.e. a measurement greater than three times the upper limit of normal). Etoricoxib had fewer discontinuations for hepatic adverse events, less increase in serum transaminase levels and fewer events meeting criteria for hepatotoxicity.

FDA Reviews of Current Submission—

Executive Summary from Statistical Review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL SAFETY STUDIES

NDA Numbers:	21-389 and 21-772
Drug Name:	Arcoxia (etoricoxib)
Dosage Form:	Oral
Dosage Strengths:	30 mg tablet
	60 mg tablet
Indication(s):	Symptomatic treatment of osteoarthritis
Applicant:	Merck
Submission Date:	October 27, 2006
Date Review Completed:	March 8, 2007
PDUFA Date:	April 27, 2007
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Yu-te Wu, Ph.D.
Concurring Reviewers:	George Rochester, Ph.D., RAC
Medical Division:	Division of Anesthesia, Analgesia & Rheumatology Products
Clinical Team:	Robert Shibuya, M.D. , Clinical Reviewer
	Sharon Hertz, M.D., Deputy Division Director
Project Manager:	Kimberly Compton, R.Ph.

Keywords: cardiovascular adverse event, safety study, Cox regression, pooling, subgroup analysis, MEDAL program

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The purpose of this review is to assess the effects of etoricoxib (ARCOXIA) on cardiovascular (CV), gastrointestinal (GI), renal-vascular outcomes (particularly, hypertension-related, edema-related events and congestive heart failure in the Multinational Etoricoxib Versus Diclofenac Arthritis Long-Term Study (MEDAL) program. Special attention was given to the subgroup of patients with osteoarthritis (OA) taking etoricoxib 60mg daily, since the proposed indication and dosage are for the treatment of patients with OA at the 60 mg dose. There is also a request to use a 30 mg dose but safety data for this dose was not collected in this study. The MEDAL program, consisting of three randomized clinical trials, was designed to further characterize the CV safety of etoricoxib (60 mg or 90 mg) in the treatment of subjects with OA or rheumatoid arthritis (RA). Study results of the MEDAL program were submitted to the agency primarily to address the CV safety issues of etoricoxib raised in the previous review cycle. The program consisted of 34,701 OA or RA patients randomized (1:1) to take either etoricoxib (60 or 90 mg for OA, and only 90 mg for RA) or diclofenac (150 mg total daily dose).

In the protocol, the primary CV safety endpoint was confirmed thrombotic event. However, during study design and protocol review the agency did not agree with applicant's definition of the primary outcome. This review considers the primary endpoint definition for CV assessment as defined by the confirmed Antiplatelet Trialists' Collaboration (APTC) combined events. The secondary CV endpoints, confirmed thrombotic events and confirmed arterial events, are also analyzed. For all CV endpoints, the intent-to-treat population (ITT, defined as all patients as randomized and took at least 1 dose of study drug and had at least one investigator follow-up contact at any time point after the start of study medication) is the primary analysis population, rather than per-protocol population as pre-specified by applicant.

For renal-vascular and GI events, mITT (28) population (defined as all patients randomized and took at least 1 dose of study drug, had investigator contact at any time after start of study medication and events occurred within 28 days of the last dose of study medication) is the primary analysis population since the adverse experiences that occurred beyond 28 days of therapy discontinuation were not planned for collection as specified in the protocol. All available populations are analyzed and examined for consistency of conclusions.

This study was subject to the same blinded external adjudication process as the entire etoricoxib development program. Potential thrombotic CV serious adverse experiences were adjudicated in a blinded fashion by an expert external Vascular Event Committee. Potential upper or lower GI clinical events were adjudicated in a blinded fashion by an external expert GI Case Review Committee

Using either the confirmed APTC, the confirmed thrombotic or arterial events, etoricoxib (60 and 90 mg, OA and RA pooled) appears to have similar APTC, thrombotic or arterial outcomes compared to diclofenac, meeting the pre-specified non-inferiority criterion which was defined as the upper bound of 95% confidence interval of risk ratio (etoricoxib/diclofenac) less than 1.3 for all CV endpoints. These findings were consistent in the ITT, mITT(28) and per-protocol populations. Etoricoxib (60 and 90 mg, OA and RA pooled) was associated with a significantly higher risk of renal-vascular events, including hypertension-related, edema-related and congestive heart failure (CHF) events, compared to diclofenac. Most patients who had renal-vascular events occurred did not develop confirmed APTC, confirmed thrombotic or arterial events. For those subjects with renal-vascular events, 1.6% of subjects also

experienced an APTC event, 2.4% of subjects experienced confirmed thrombotic events, and 2.04% of subjects who developed confirmed arterial events. The analysis was conduced based on the Cox proportional hazards model pooling all data in the MEDAL program, stratifying by the use of low dose aspirin, the type of disease (OA/RA) and study.

Etoricoxib (60 and 90 mg, OA and RA pooled) demonstrates a significantly superior upper GI outcome to diclofenac, based on the hazard rates of confirmed upper GI clinical events (perforations, ulcers, and bleeds). The treatment groups were well balanced with respect to the use of gastroprotective agents (GPA) in three studies with the range of 18% to 60% of patients taking GPAs. In the pooled MEDAL program, 50.5% and 50.7% of patients took GPA in the etoricoxib and diclofenac groups, respectively. Therefore, the use of GPAs should not have much impact on the evaluation of confirmed upper GI events. Etoricoxib (60 and 90mg, OA and RA pooled) had a numerically lower rate of confirmed lower GI outcome (perforations, obstructions, bleeds; POBs) compared to diclofenac, but the difference was not statistically significant.

Attention was specifically given to the subgroup of OA patients taking etoricoxib 60mg daily which is the proposed indication and dosage. In the MEDAL program etoricoxib 60 mg was comparable to diclofenac for the confirmed thrombotic events with an estimated relative risk (RR) and (95% CI) of 1.06(0.86, 1.31); 1.07(0.83, 1.37) for APTC; and 1.01(0.80, 1.26) for confirmed arterial events. However, etoricoxib 60mg was associated with a higher risk of hypertension- and edema-related events compared to diclofenac with RR (95% CI) 1.21(0.96, 1.52) for hypertension-related events and 1.09 (0.75, 1.59) for edema-related events. In terms of GI events, despite the use of GPAs etoricoxib was associated with a lower risk of confirmed upper GI events compared to diclofenac with RR (95% CI) 0.74 (0.52, 1.04). Etoricoxib was associated with a lower risk of confirmed lower GI events compared to diclofenac with RR (95% CI) 0.79 (0.48, 1.30). The risk of etoricoxib to diclofenac for all endpoints examined was dose-related, i,e., relative to diclofenac, etoricoxib 90mg group was associated with a higher risk compared to etoricoxib 60mg group.

1.2 Brief Overview of Clinical Studies

In the first review cycle, the applicant filed NDA 21-389 on Dec 30, 2003, and NDA 21-772 on April 30, 2004, for etoricoxib and requested approval for indications of osteoarthritis (OA), rheumatoid arthritis (RA), acute gouty arthritis, ankylosing spondylitis, chronic low back pain, acute pain in adults and primary dysmenorrheal for 60, 90 and 120 mg tablets. After the first review cycle, the agency issued approvable letters for both NDAs that requested additional long-term safety data to further characterize the safety profile of etoricoxib. The MEDAL program was designed primarily to characterize the CV safety profile of etoricoxib relative to the traditional NSAID diclofenac. The program consisted of three randomized, double-blind, active comparator-controlled clinical studies – Etoricoxib Versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness Study I (EDGE I), MEDAL and Etoricoxib Versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness Study II (EDGE II). In the current submission dated October 27, 2006, the applicant provided the results of the MEDAL program as a single response to first address approvability issues on CV safety for etoricoxib 30 or 60 mg once daily for the symptomatic treatment of osteoarthritis. The MEDAL program did not include patients treated with 30 mg. When MEDAL program was designed, the 30 mg dose was not considered in the development program. The MEDAL program was set up to address CV concerns for the doses and indications desired in the previous cycle.

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