Food and Drug Administration
Center for Drug Evaluation and Research

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**SUMMARY MINUTES**
**ARTHRITIS ADVISORY COMMITTEE**

**April 20, 1999**
Holiday Inn Gaithersburg
2 Montgomery Village Avenue, Gaithersburg, MD

**Members Present**
Steven B. Abramson, M.D., Chair
Daniel J. Lovell, M.D., M.P.H.
David E. Yocum, M.D.
Leona Malone, MSW
Frank Pucino, Jr., Pharm.D.

**Consultants**
Ildy M. Katona, M.D.
Janet D. Elashoff, Ph.D.
Kevin R. McConnell, M.D.

**Members Absent**
E. Nigel Harris, M.D.

**Executive Secretary**
Kathleen R. Reedy

**FDA Participants**
Robert DeLap, M.D.
John Hyde, M.D.
Maria Lourdes Villalba, M.D.
Mordechai Averbuch, M.D.
Lawrence Goldkind, M.D.
Juan Carlos Palayo, M.D.
Susan D. Wilson, D.V.M., Ph.D.
Dennis Bashaw, Pharm.D.
Qian Li, Ph.D.

**Guest Experts**
James Scheiman, M.D.
John Wallace, Ph.D.

These summary minutes for the April 20, 1999 meeting of the Arthritis Advisory Committee were approved on 6/28/99.

I certify that I attended the April 20, 1999 meeting of the Arthritis Advisory Committee and that these minutes accurately reflect what transpired.

Kathleen R. Reedy,
Executive Secretary

Steven B. Abramson, M.D.
Chairperson

The Arthritis Advisory Committee met at the Holiday Inn Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, MD on April 20, 1999 at 8am to discuss NDA # 21-042, Vioxx™ (rofecoxib) Merck Research Laboratories. The meeting was attended by approximately 400 people. The Advisory Committee members had been provided a background document from both the sponsor and the Agency approximately 20 days before the meeting.

The meeting was called to Order at 8:05 by Steven Abramson, M.D., Acting Chair, and after all participants at the table were introduced, the Meeting Statement was read by Kathleen Reedy, Executive Secretary.

The Merck Research Laboratories Presentation included:

Introduction: Robert Silverman, M.D., Ph.D.
Program Hypotheses: Beth Seidenberg, M.D.
COX-2 Specificity
Efficacy in Osteoarthritis
Efficacy in Acute Analgesia
Human Gastrointestinal Safety: Thomas Simon, M.D.
General Safety and Tolerability: Beth Seidenberg, M.D.
Summary and Conclusions

The FDA Presentation consisted of:

Introduction and OsteoArthritis: Maria Lourdes Villalba, M.D.
Management of Acute Pain: Mordechai Averbuch, M.D.
Nonclinical Safety Evaluation: Susan D. Wilson, DVM, Ph.D.
PharmacoKinetics: E. Dennis Bashaw, PharmD.
Gastrointestinal Safety: Lawrence Goldkind, M.D.
Statistical Review: Qian Li, Ph.D.
Vascular and Renal Safety: Juan Carlos Pelayo, M.D.

There were no speakers for the Open Public Hearing.

Discussion and Questions were addressed as follows:

<u>Efficacy</u>

1. Should rofecoxib be approved for the indication of the treatment of the signs and symptoms of OA? Yes: 8 No: 0

2. Does the committee agree with the proposed dose of 12.5 to 25 mg for OA? Yes

a) If so, are there concerns about the potential for, and the possible risk of, using more than the proposed dose?

Yes, there is concern about "dose creep" and discussion followed.

b) What, if any, information about dosing needs to be conveyed in the labeling other than providing a recommended dose?

Recommend beginning with 12.5 and increasing to 25mg dose, the effective dose for osteoarthritis. There was consensus that only information regarding adverse events that is known, learned in trials, should be included in labeling.

3. What comparability conclusions are appropriate concerning rofecoxib and active controls?

Comparability conclusions that present a clinical difference that are clinically comparable; clinical superiority is not shown.

Does the committee have any comments on the criteria used for clinical comparability (± 10 mm on a 100-mm VAS, or ± 0.5 on a Likert scale)?

There was discussion that the scale be less than half the difference between placebo and drug to be considered comparable; and the point estimate closer to be called equivalent or clinically comparable.

4. Does the committee concur that there is adequate evidence to approve rofecoxib as an analgesic? Yes: 6 Qualified Yes: 2 No: 0

If so, what dose and dosing interval should be recommended for managing acute pain?

Based on the submitted data, 50 mg dose for maximum of five days, the standard effective dose for acute pain. There is a risk of adverse events beyond the 5 days. Labeling could suggest discontinuation after five days.

5. In light of prior AAC discussions proposing separate consideration of chronic pain, should there be any subspecification of the pain indication for rofecoxib?

No, as there is no data or evidence as yet for chronic pain dosing.

What dosing, if any, should be recommended for management of chronic pain?

For chronic pain, the standard effective dose for osteoarthritis, 12.5-25 mg.

<u>Gastrointestinal Safety</u>

6. At prior AAC meetings on this subject, endoscopic studies have been viewed as surrogates of clinically meaningful endpoints. Given that rofecoxib, in these endoscopic studies, has demonstrated consistent statistical superiority to only one NSAID (ibuprofen),

a) What comparisons should be allowed in the labeling between rofecoxib and ibuprofen?

Consensus that ibuprofen is acceptable as a general representative of an NSAID comparator in endoscopic studies. Broader profiles are needed and comparator NSAIDs must be based on specific head to head data.

b) How should the results with different doses be interpreted?

Include label reference that comparator is ibuprofen.
Dose specific information, particularly with 50 mg dose be included and a placebo control trial reported.

c) Can these data be extrapolated to make comparisons between rofecoxib and other NSAIDs as well?

No need for large endoscopic studies with any other comparator, however the label statement should note this limitation.
Comparator information should be dose specific in the labeling.
PUBS information should be split stating the placebo information.
Consider the possibility of 3 subsets of information: endoscopy, gi side effects (including clinical peptic ulcer disease) and serious gi adverse events (perforation, obstruction, hemorrhage).

7. An underlying concept of the rofecoxib development program has been that COX-2 selectivity would provide enhanced GI safety. While the rofecoxib studies completed to date suggest that endoscopically diagnosed ulcers may occur less frequently with rofecoxib treatment compared to an NSAID comparator, comparisons of the rates of "clinically significant" GI adverse events are less clear due to the small number of such events in studies to date.

a) Is the NSAID warning template still appropriate, pending completion of appropriately powered trials to assess the incidence of significant GI events with rofecoxib compared to one or more NSAID products? Yes: 8 No: 0

b) should qualifications be made to the NSAID GI warning template, while noting the limited experience with the new molecular entity? Yes: 8 No: 0

State only what is known from trial experience.
List esophageal ulcer side effects found with 50 mg. dose.

8. NSAID labeling recommends against concurrent use of aspirin and NSAIDs. Rofecoxib apparently lacks an antiplatelet effect; but there are few data from the one clinical study in which patients were permitted to use aspirin concurrently with rofecoxib and there have been no endoscopic studies in which aspirin and rofecoxib were used together. What recommendations, if any, should be made concerning use of prophylactic low dose aspirin concurrently with rofecoxib?

There was consensus that the label should describe only what we know.
State the common scenario and the fact that there is no data for this specific concurrent use.

<u>Renal Safety</u>

9. The overall renal effects of rofecoxib at the proposed dose for OA (12.5 to 25 mg), including the incidence of peripheral edema and other renal adverse effects, appear to be similar to those of currently approved NSAIDs. However, it appears that chronic dosing of 50 mg. QD or higher might be associated with increased renal adverse effects.

a. Do you agree with this assessment?
Yes: 7 (four with reservations). NO: 1

b. How should any conclusion be reflected in labeling?
Describe and differentiate the peripheral edema that might be expected in OA. Higher doses are not prescribed for more than five days, edema of concern could be described. Edema is of more than moderate concern.

10. The data on serum chloride and bicarbonate included in the NDA were not extensive, and there were no data on phosphorus and magnesium in the initial submission.
    a. How important is the missing information to the overall interpretation of the renal safety of rofecoxib? Not of great consequence.

    b. Should additional safety studies be required? Consensus is No.

    c. How should the current state of knowledge be reflected in labeling?
    Not included in the labeling.

Other Issues

11. What clinical recommendations should be made regarding use of rofecoxib in patients with moderate hepatic insufficiency?
    Inadequate data to discuss. More studies requested.

    If additional PK studies are needed, what should they be (single-dose or multiple dose)?
    Inadequate data to discuss, but multipoe dose, steady state data was requested.

12. Please provide recommendations for any Phase 4 studies that should be required for rofecoxib.
    studies in elderly
    pediatric studies
    co morbid conditions
    analysis of dosage creep:
        50 mg dose over time
        RA studies
    serious gastrointestinal clinical adversity
    expanded study of reproductive system effect

The meeting was adjourned at 5:00pm.

Kathleen Reedy, Health Scientist Administrator
Executive Secretary, Arthritis Advisory Committee