Arthritis Advisory Committee
Food and Drug Administration
Center for Drug Evaluation and Research

Holiday Inn Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, MD

April 20, 1999
NDA # 21-042, **Vioxx™** (rofecoxib) **Merck** Research Laboratories

Agenda

8:00 Call to Order, Introductions: Steven Abramson, M.D., Chair,
Arthritis Advisory Committee
Meeting Statement: Kathleen Reedy, Executive Secretary,
Arthritis Advisory Committee

8:15 Merck Research Laboratories Presentation
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

10:00 Break

10:15 FDA Presentation
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.

11:25 Open Public Hearing

12:00 Lunch

1:00 Discussion and Questions

Break

5:00 Adjourn

Arthritis Advisory Committee
Food and Drug Administration
Center for Drug Evaluation and Research
Holiday Inn Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, MD

April 20-21, 1999
NDA # 21-042, **Vioxx** (rofecoxib) **Merck** Research Laboratories
Questions

Efficacy

1. Should rofecoxib be approved for the indication of the treatment of the signs and symptoms of OA?

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

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

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

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

   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)?

4. Does the committee concur that there is adequate evidence to approve rofecoxib as an analgesic?

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

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

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

Gastrointestinal Safety

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?

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

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

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?

   b) Or should qualifications be made to the NSAID GI warning template, while noting the limited experience with the new molecular entity?

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?

Renal Safety

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?

   b. How should any conclusion be reflected in labeling?

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?

   b. Should additional safety studies be required?

   c. How should the current state of knowledge be reflected in labeling?

Other Issues

11. What clinical recommendations should be made regarding use of rofecoxib in patients with moderate hepatic insufficiency?

    If additional PK studies are needed, what should they be (single-dose or multiple dose)?

12. Please provide recommendations for any Phase 4 studies that should be required for rofecoxib.