



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 46,894

Merck Research Laboratories
Attention: Ned Braunstein, M.D.
Director, Regulatory Affairs
P.O. Box 2000 RY 33-720
Rahway, NJ 07065-0900

Dear Dr. Braunstein:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Vioxx (rofecoxib) tablets, 12.5 mg, 25 mg, 50 mg.

We have completed the clinical review of your protocol entitled: "Prospective Combined Analysis of Thrombotic Cardiovascular Events in 3 Randomized, Double-Blind, Placebo-Controlled Studies of Rofecoxib in Patients at Risk of Developing Recurrent Adenomatous Colon Polyps, Recurrent Colon Cancer, or Prostate Cancer/Protocol No. 203-00". Provided below are the Division responses to the questions that were submitted regarding Protocol No. 203-00.

SPONSOR QUESTIONS with FDA RESPONSE

- 1A. Does the Agency agree that a prospective combined analysis of 3 similarly conducted, long-term studies comparing a single dose of rofecoxib (25 mg) to placebo would provide clinically important information about the effects of rofecoxib on the incidence of thrombotic events and would therefore constitute a cardiovascular outcomes study with rofecoxib?

FDA Response:

A study with the proposed exposure (size and duration) would provide clinically important safety information about rofecoxib.

- 1B. Does the Agency agree with MRL's plans to combine the cardiovascular data from the APPROVe, VICTOR, and Prostate Cancer Prevention studies as described in the protocol?

FDA Response:

- a. **Conceptually a meta-analysis is reasonable.**

- b. However, the issue of homogeneity needs to be addressed before pooling the three studies for analysis. The sponsor should do appropriate tests for “combinability”.
 - c. Agency suggests evaluation of the KM curves of each study as well as careful analysis of hazard rate over time.
 - d. The sponsor is advised to add a study-by-treatment interaction term to the model.
 - e. Conceptually a safety analysis cannot be restricted to prespecified definitions of “success” or “noninferiority”.
2. The patients in the APPROVe, VICTOR AND Prostate cancer prevention studies are anticipated to represent a typical spectrum of patients at risk for thrombotic cardiovascular events and it is anticipated that 10 to 20% of patients will be taking low-dose aspirin for cardiovascular prophylaxis. Does the Agency agree that the patient populations being studied in the APPROVe, VICTOR, Prostate Cancer Prevention studies are appropriate for the study of the cardiovascular safety of rofecoxib?

FDA Response:

Given the ethical constraints of studying safety compared to placebo, the use of the populations enrolled in the proposed therapeutic trials is reasonable. Although a high risk population is generally optimal to study risk, a minimum of 20% patients taking low dose ASA for CV prophylaxis appears acceptable.

3. Does the Agency agree that the primary analysis of confirmed thrombotic cardiovascular events for non-inferiority of rofecoxib vs. placebo (primary hypothesis) should be performed in a Per-Protocol population? Rules for excluding patients from the Per-Protocol population will include lack of compliance and use of non-study NSAIDs. The complete definition will be prespecified in the DAP.

FDA Response:

No.

- a. The Agency does not agree with the proposal of a per-protocol analysis as the only primary analysis. Even for a non-inferiority trial, the intention-to-treat (ITT) analysis is important because it preserves randomization and avoids bias introduced by PP exclusion criteria. A modified ITT is acceptable. Both ITT and PP analyses are important.
- b. An outline of the analysis plan should be submitted with the original protocol (only minor changes in details should be left for the final DAP with justification for changes made).

Note: The Division of Cardio-renal products is uncomfortable with the use of a non-inferiority trial. For claims related to the CV system, direct discussion with the Division of Cardio-renal products is recommended.

4. Does the Agency agree that the primary analysis for superiority of rofecoxib versus placebo (secondary hypothesis) should be performed on the modified ITT population as defined in the protocol?

FDA Response:

Yes.

5. MRL proposes that for the non-inferiority hypothesis, the upper comparability bounds for the 95% CI of the hazard ratio should be 1.30. Assuming a true underlying HR of 1.00, approximately 611 confirmed thrombotic events need to be observed to provide 90% power to yield the upper limit of the 95% CI for $HR < 1.30$. Satisfying this criteria would require an observed HR no larger than approximately 1.16. MRL anticipates that 611 confirmed events in the per protocol population will be accrued by 2006. Does the Agency concur with these proposed design specifications?

FDA Response:

No. The Agency does not agree with the proposed non-inferiority bounds. For serious adverse events, such as CV thrombotic events, a 30% delta appears to be unacceptably wide. The agency agrees that hypotheses regarding relative risk are appropriately prespecified by the Sponsor. However, review by the agency and labeling changes relative to safety cannot be limited to prespecified hypotheses.

The proposed protocol with this size and duration will provide an extremely valuable and robust safety database. However, since the hazard ratio of CV-thrombotic events may not be constant (as suggested by the VIGOR study) and the timing of the occurrence of events is not known the Agency can not commit to agree on what would be "non-inferior". The sponsor may define important time intervals for which the hazard ratio should be estimated and propose a statistical analysis plan for each of these intervals. The Sponsor in this regard may propose different appropriate non-inferiority margins for different time intervals. As non-inferiority is required at each of the proposed time intervals, no correction for multiplicity would be necessary.

6. MRL proposes analyzing the CV data from these protocols after approximately 611 events in the Per-Protocol population have been confirmed and submitting a CSR and labeling supplement based on this analysis. It is anticipated that 2 of the studies (VICTOR, and the Prostate Cancer Study) will be ongoing at that time. MRL proposes but does not anticipate submitting labeling supplements based on the updates unless the data supported substantive changes. Does the Agency agree that the analyses described above and based on the first approximately 611 events could be described in product labeling?

FDA Response:

No. Since the hazard rate for cardiovascular event may increase with time, the Agency is concerned that the first 611 events may not reflect the true hazard ratio at a later timepoint. The primary analysis should be done at the end of the study although a blinded interim analysis after prespecified goal of both minimum exposure (in terms of numbers of patients and duration) and number of events exposure has been achieved may be discussed with the

Agency in reference to inclusion in labeling. A per-protocol analysis should be confirmatory of the primary analysis. In addition, the sponsor should do appropriate secondary analyses for evaluating time related-risk estimates for patients who are at high risk for CV events, and for regional differences.

7. Does the Agency agree that performing the studies and analyses described in the protocol would result in the removal of the statement in the US product circular that "Prospective studies specifically designed to compare the incidence of serious CV events in patients taking VIOXX versus NSAID comparators or placebo have not been performed" and that the data from this prespecified combined analysis could be described in product labeling as data from a CV Outcome Study?

FDA Response:

See answers to questions 1 to 6.

8. Does the Agency agree that the data from this study would be relevant to revising the Precaution, Cardiovascular Effects section of the product circular?

FDA Response:

Yes.

9. MRL proposes that single External Safety Monitoring Board (ESMB) will monitor all aspects of safety in the APPROVe and Prostate Cancer Prevention Studies. The VICTOR study is being conducted by Oxford and has its own Data Safety Monitoring Committee (DSMC) that will monitor safety in that study. However, to ensure that cardiovascular safety information from all 3 studies is considered when assessing patient safety, MRL has proposed that the same ESMB monitoring APPROVe and the Prostate Cancer Prevention study will also monitor the cardiovascular safety data from all three studies. This ESMB will communicate its findings at each meeting to the VICTOR DSMC. Does the Agency agree with this strategy for ensuring patient safety in these studies?

FDA Response:

Yes.

If you have any questions, call Barbara Gould, Project Manager, at 301 827-2090.

Sincerely,

{See appended electronic signature page}

Lawrence Goldkind, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Lawrence Goldkind
12/19/02 04:59:02 PM