

Robert E. Silverman, M.D., Ph.D.  
Senior Director  
Regulatory Affairs

ORIGINAL

Merck & Co., Inc.  
P.O. Box 4  
West Point PA 19486  
Fax 610 397 2516  
Tel 610 397 2944  
215 652 5000

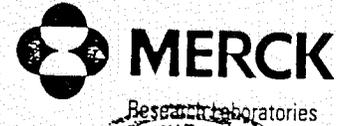
These copies are OFFICIAL FDA Copies  
not desk copies.

March 10, 1999

NEW CORRESP

Robert J. DeLap, M.D., Acting Director  
Division of Anti-Inflammatory, Analgesic and  
Ophthalmic Drug Products, HFD-550  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

NC



Dear Dr. DeLap:

**NDA 21-042: VIOXX™ (Rofecoxib) Tablets  
Response to FDA Request**

Reference is made to the above New Drug Application (NDA) and a teleconference between Merck Research Laboratories [MRL] and FDA on March 5, 1999 during which the Agency statistician (Dr. Li) requested clarification concerning patient discontinuations in Protocols 034 and 035.

By this letter and attachments, MRL is responding to the Agency's request.

**FDA Request:** The FDA statistician (Dr. Qian Li) pointed out two errors on the Patient Accounting Table 19 in the Protocol 034 Clinical Study Report (CSR) provided in the original NDA. The percents of patients discontinuing due to clinical adverse experience in the 12.5 and 25 mg MK-0966 groups were marked with "\*" indicating significant difference from diclofenac. Dr. Li indicated that her analysis revealed no significant difference. In addition, she requested that these tables be run for Week 6 and Week 12 data (they are run for the 0-24 week data, the last time point analyzed, in the CSRs) for each of Protocols 034 and 035.

**MRL Response:** The "\*" next to the percents of patients discontinuing due to Clinical adverse experience in the 12.5 and 25 mg MK-0966 groups in Table 19 of the Protocol 034 CSRs were typographical errors: Merck apologizes for them. The rates of discontinuation due to clinical adverse experience's were found to not be statistically significantly ( $p > 0.10$ ) different among the treatments. Also, the footnote attached to "Other reasons" in Table 19 is incorrect. It should read "Includes reasons 'Patient discontinuation' and 'Patient moved'."

The data for discontinuation tables for Weeks 8 and 12 for each of Protocols 034 and 035 are attached. Since there was no scheduled Week 6 visit in these protocols, the Week 8 visit was substituted. In addition, the reasons "Patient discontinuation" and "Patient moved" are substituted for "Other reasons" in the Protocol 035 results in order to be consistent with the

Robert J. DeLap, M.D., Acting Director  
NDA 21-042: VIOXX (Rofecoxib) Tablets

Page 2

results presented for Protocol 034. The patterns of discontinuations were generally similar between treatment groups to those seen in the 24 week tables.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,



Robert E. Silverman, M.D., Ph.D.  
Senior Director, Regulatory Affairs

q/shilling/tr614

Federal Express #1

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1  
Dr. Q. Li, HFD-550, CRP2 N327, Federal Express #1

Robert E. Silverman, M.D., Ph.D.  
Senior Director  
Regulatory Affairs

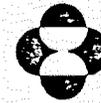
ORIGINAL

Merck & Co., Inc.  
P.O. Box 4  
West Point PA 19486  
Fax 610 397 2516  
Tel 610 397 2944  
215 652 5000

These copies are  
OFFICIAL FDA Copies  
not desk copies

March 10, 1999

NEW CORRESP



**MERCK**

Research Laboratories

Robert J. DeLap, M.D., Acting Director  
Division of Anti-Inflammatory, Analgesic and  
Ophthalmic Drug Products, HFD-550  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

NC



Dear Dr. DeLap:

**NDA 21-042: VIOXX™ (Rofecoxib) Tablets  
Response to FDA Request**

Reference is made to the above New Drug Application (NDA) and a teleconference between Drs. R. Silverman, T. Simon, L. Oppenheimer and E. Floyd (Merck Research Laboratories [MRL]) and Drs. Li, Lin and Ms. S. Cook (FDA) on March 9, 1999 during which the Agency requested clarification of issues related to Protocols 044 and 045.

By this letter, MRL is providing the requested clarification.

**FDA Request:** The clinical study report for Protocol 044 (page 72) states: "Fifty-two patients did not have treatment phase endoscopy, and thus could not be included in any endoscopic endpoint analyses [4.3]. Sensitivity analyses were performed to evaluate the impact of these missing data." The section on sensitivity analyses (page 96) does not clearly identify how these 52 patients are handled.

Similarly, the clinical study report for Protocol 045 (page 72) states: "Thirty-seven patients did not have treatment phase endoscopy, and thus could not be included in any endoscopic endpoint analyses [4.3; 4.10.1]. Sensitivity analyses were performed to evaluate the impact of these missing data [4.1.10; 4.1.11]." The section on sensitivity analyses (page 99) is similarly unclear with regard to the 37 patients with no treatment phase endoscopy data.

**MRL Response:** Two sets of sensitivity analyses were provided for each study. For Protocol 044, these are described on Page 96. The first paragraph describes analyses for which results were imputed to patients who were discontinued due to GI AE. The second paragraph provides results for all patients with missing data.

For Protocol 044, the second paragraph refers to an analysis of 129 patients with missing data. The 52 patients with no treatment phase endoscopy are among these 129 patients; a separate sensitivity analysis of these 52 patients was not performed. (The definition of missing data for this analysis is given on page 38).

Similarly, for Protocol 045, the second paragraph on page 99 refers to an analysis of 125 patients. The 37 patients with no treatment phase endoscopy are among these 125 patients; a separate sensitivity analysis of these 37 patients was not performed. (The definition of missing data for this analysis is given on page 41).

We need to identify a typographical error in the definition on pages 38 of Protocol 044 and page 41 of 045. This occurs in the definition of nonmissing data for the second sensitivity analysis, and pertains to the analysis at Week 24. The current sentence for Protocol 044 is, "A patient was defined to have nonmissing data for the Week 24 analysis if he/she had an ulcer before Week 23 (thus, this patient was assumed to have an ulcer at Week 24 also), or he/she had an endoscopy after Week 23 **and this endoscopy showed no ulcer**" [emphasis added]. The phrase "and this endoscopy showed no ulcer" should not be present at the end of this sentence. It should read, "A patient was defined to have nonmissing data for the Week 24 analysis if he/she had an ulcer before Week 23 (thus, this patient was assumed to have an ulcer at Week 24 also), or he/she had an endoscopy after Week 23". The phrase "and this endoscopy showed no ulcer" was inadvertently copied from previous text discussing a different situation [Week 12, in the same paragraph].

For Protocol 045, the current sentence is, "A patient was defined to have nonmissing data for the Week 24 analysis if he/she had an ulcer before Week 23 (thus this patient was assumed to have ulcers at Week 24 also), or he/she had an endoscopy after Week 23 **and this endoscopy showed no ulcer**" [emphasis added]. The phrase "and this endoscopy showed no ulcer" was inadvertently copied from previous text discussing a different situation [Week 12, in the same paragraph].

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Robert J. DeLap, M.D., Acting Director  
NDA 21-042: VIOXX (Rofecoxib) Tablets

Page 3

If you have any questions or need additional information please contact Robert Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,



Robert E. Silverman, M.D., Ph.D.  
Senior Director, Regulatory Affairs

q/shilling/ltr/613

Federal Express #1

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1  
Dr. Q. Li, HFD-550, CRP2 N347, Federal Express #1

Robert E. Silverman, M.D., Ph.D.  
Senior Director  
Regulatory Affairs

**DUPLICATE**

Merck & Co., Inc.  
P.O. Box 4  
West Point PA 19486  
Fax 610 397 2516  
Tel 610 397 2944  
215 652 5000

March 12, 1999

**These copies are OFFICIAL FDA Copies  
not desk copies.**

**NDA ORIG AMENDMENT**

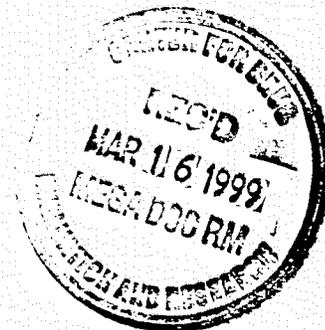


**MERCK**

Research Laboratories

Robert J. DeLap, M.D., Acting Director  
Division of Anti-Inflammatory, Analgesic and  
Ophthalmic Drug Products, HFD-550  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

*BM*



Dear Dr. DeLap:

**NDA 21-042: VIOXX™ (Rofecoxib) Tablets  
Response to FDA Requests**

Reference is made to the above New Drug Application (NDA) and to an e-mail sent to Dr. R. Silverman (Merck Research Laboratories [MRL]) from Ms. S. Cook (FDA) on March 1, 1999 with several requests from the Medical Officer.

The MRL responses to the first and second FDA comments were provided under separate cover on March 10, 1999.

By this letter, we are responding to the Agency's third and fourth requests.

**FDA Comments 3 and 4:** For all patients, provide life table analyses of the following adverse events at 6 weeks, 12 weeks, 6 months, one year and 86 weeks. (Attached is an example of the format to follow).

**3.1 - Edema and related events:**

Edema / Fluid retention / Lower extremity edema / Peripheral edema / Upper extremity edema and Weight gain

**3.2 - Cardiovascular system**

a) Hypertension (HTN)/ Blood pressure increased / systolic HTN /diastolic HTN / HTN uncontrolled with medication/ Hypertensive crisis/ Uncontrolled HTN

b) Acute myocardial infarction / Myocardial infarction / Unstable angina

c) Angina pectoris / Coronary artery disease

d) Cerebrovascular accident / Transient ischemic attack

3.3 - Digestive system

- a) Heartburn
- b) Nausea / Vomiting
- c) Oral lesion / Oral ulcer

3.4 - Psychiatric disorder:

- a) Anxiety
- b) Depression

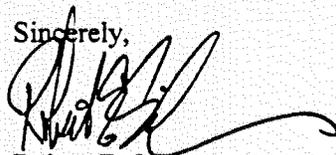
4. - Provide the complete survival analysis curves for the above adverse events, for each dose.

**MRL Response:** Responses to both requests are incorporated into the attachment.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,



Robert E. Silverman, M.D., Ph.D.  
Senior Director, Regulatory Affairs

q/shilling/tr/601b  
Attachment

Federal Express #1

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1

Robert E. Silverman, M.D., Ph.D.  
Senior Director  
Regulatory Affairs

Merck & Co., Inc.  
P.O. Box 4  
West Point PA 19486  
Fax 610 397 2516  
Tel 610 397 2944  
215 652 5000

**DESK COPY**

March 16, 1999

Robert J. DeLap, M.D., Acting Director  
Division of Anti-Inflammatory, Analgesic and  
Ophthalmic Drug Products, HFD-550  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



Dear Dr. DeLap:

**NDA 21-042: VIOXX™ (Rofecoxib) Tablets  
Response to FDA Request**

Reference is made to the above New Drug Application (NDA) and an e-mail to Dr. R. Silverman (Merck Research Laboratories[MRL]) on March 11, 1999 from Ms. S. Cook (FDA) with a request from Dr. Goldkind.

By this letter, we are responding to the Agency's request.

**FDA Comment:** Please provide the data on GI adverse events, NSAID adverse events, the nausea and vomiting and heartburn data and discontinuation due to GI adverse events. Please analyze by dose and endpoints in study 069 for PUBs and AEs.

**MRL Response:** The requested data and analyses are provided in the attachment.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

A handwritten signature in black ink, appearing to read 'Rob Silverman'.

Robert E. Silverman, M.D., Ph.D.  
Senior Director, Regulatory Affairs

q/shilling/tr/616  
Attachment

Federal Express #1

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1  
Dr. Lawrence Goldkind, HFD-180, PKLN 6B-24, Federal Express #2

Robert E. Silverman, M.D., Ph.D.  
Senior Director  
Regulatory Affairs

ORIGINAL

Merck & Co., Inc.  
P.O. Box 4  
West Point PA 19486  
Fax 610 397 2516  
Tel 610 397 2944  
215 652 5000

These copies are OFFICIAL FDA Copies  
not desk copies.

March 16, 1999

Robert J. DeLap, M.D., Ph.D., Acting Director  
Division of Anti-Inflammatory, Analgesic and  
Ophthalmic Drug Products, HFD-550  
Center for Drug Evaluation and Research (ODE V)  
Food and Drug Administration  
201 Corporate Blvd.  
Baltimore, MD 20850



NEW CORRESP  
NC



NDA 21-042: VIOXX™ (Rofecoxib) Tablets  
General Correspondence

Dear Dr. DeLap:

Reference is made to the above New Drug Application and the forthcoming FDA Arthritis Advisory Committee Meeting on April 20, 1999. In preparation for the meeting, MRL has prepared responses to anticipated issues which may be addressed at the Advisory Committee Meeting. By this letter and attachments, MRL is providing the Agency with advanced responses to the following issues:

Issue #1: Are there any pharmacokinetic differences among race categories following oral administration of MK-0966 that suggest a need for dosage adjustments?

Response: A combined analysis pooling the pharmacokinetic data from several studies was conducted (Attachment 1). The pharmacokinetic data was obtained from the 12.5mg oral tablet data from Protocol #070, the 25-mg oral tablet data from Protocols #048, #052, #070 and #076 and the 50-mg oral tablet data from Protocols #037 and #043. The dose-adjusted (to 50-mg) AUC<sub>(0-∞)</sub> least-square mean on the Analysis of Covariance model for Blacks, Hispanic and White race categories was 8294, 7227 and 7227 respectively. Relative to the White category, the Black and Hispanic adjusted mean ratios (Black/White) and (Hispanic/White) was 1.15 and 1.09, respectively with corresponding 90% confidence intervals of (1.02, 1.29) and (0.97, 1.22). The results for C<sub>max</sub> showed virtually no difference among race categories; moreover, similar results were also obtained with respect to T<sub>max</sub> and terminal half-life. Therefore, no dosage adjustment by race is indicated.

BEST POSSIBLE COPY

**Issue #2:** Are there any differences in pharmacokinetic comparisons of separate mild and moderate hepatic insufficiency patients versus healthy subjects that suggest a need for dosage adjustments?

**MRL Response:** Pharmacokinetic comparisons of separate mild (Child-Pugh Scores 5-6) and moderate (Child-Pugh Scores 7-9) hepatic insufficiency patients from Protocol 057 versus healthy subjects from Protocols 037, 043, 048, and 052 were conducted using an analysis of covariance (ANCOVA) model (Attachment 2). For both oral and I.V. doses, the 90% CI of the AUC GMR for mild hepatic insufficiency versus healthy was 1.01 (90% CI 0.77 to 1.31) and was contained within the predefined clinically acceptable interval (0.50, 2.00). The AUC GMR for moderate hepatic vs. healthy was 1.69 (90% CI 1.31 to 2.19). While this would otherwise suggest an increased AUC for moderate but not mild hepatic insufficiency patients, based on the predefined clinically acceptable bounds, the original study design must be considered. The study was powered based on combining the mild and moderate patients. Thus the fact that the upper bound of the 90% CI for the AUC GMR exceeds 2.0 reflects the fact that only 4 patients are included. Had the study been designed to address the moderate patients separately, a larger number of patients would have been included. Thus, the boundaries for the confidence interval for the AUC GMR must be viewed with this in mind. Individual patient's z-scores listed in Table 9 indicate that among the moderate hepatic patients, there was a high AUC outlier (AN 001), and that two other patients had high AUC's (about 2 SD's from the mean of the normal population). However, the fourth moderate hepatic patient's AUC fell very close to the mean of the normals. Although there was a trend toward higher AUC in moderate hepatics, it was variable. Z-scores for the mild hepatic patients were consistent with falling within the expected range of the normal population AUC's. GMR's of Cmax were generally close to one and well within the [redacted] for both hepatic populations.

It should be re-emphasized that this is a post hoc analysis and Protocol 057 was not powered on separate mild and moderate hepatic insufficiency patients. The original results combining the mild and moderate hepatic insufficiency patients strongly support the stated protocol hypothesis of no clinically meaningful alteration in the pharmacokinetics of MK-0966. Therefore, no dosage adjustment for mild to moderate hepatic insufficiency is indicated.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Robert J. DeLap, M.D., Acting Director  
NDA 21-042: VIOXX™ (Rofecoxib) Tablets

Page 3

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,



Robert E. Silverman, M.D., Ph.D.  
Senior Director, Regulatory Affairs

Attachments

Federal Express #1

Desk Copy/attachments: ~~Ms. Sandra Cook~~, Project Manager, HFD-550, CRP2 N317  
2 deskcopies with hardcopy attachments

Robert E. Silverman, M.D., Ph.D.  
Senior Director  
Regulatory Affairs

DESK COPY

Merck & Co., Inc.  
P.O. Box 4  
West Point PA 19486  
Fax 610 397 2516  
Tel 610 397 2944  
215 652 5000

March 17, 1999

Robert J. DeLap, M.D., Acting Director  
Division of Anti-Inflammatory, Analgesic and  
Ophthalmic Drug Products, HFD-550  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



Dear Dr. DeLap:

**NDA 21-042: VIOXX™ (Rofecoxib) Tablets  
General Correspondence**

Reference is made to the above New Drug Application (NDA).

The recently approved product label for celecoxib contains the following GI warning information:

**“Among 5,285 patients who received Celebrex in controlled clinical trials of 1 to 6 months duration (most were 3 month studies) at a daily dose of 200 mg or more, 2 (0.04%) experienced significant upper GI bleeding, at 14 and 22 days after initiation of dosing.”**

The single figure in the warning, 0.04%, is a crude calculation (2 events/5285 OA/RA patients exposed to celecoxib) and is not annualized. The use of this approach in the celecoxib label suggests that this may be the evolving benchmark for information related to clinically significant upper GI perforations, obstructions and bleeds (“POBs”). The rofecoxib clinical development program did not prespecify such analyses. This type of analysis is subject to the very small number of events, does not account for duration of treatment, and does not meaningfully compare the test agent with NSAID comparators.

In light of the data presented in the celecoxib label, we are now providing a number of similar analyses in the Attachment (Tables 1-5), as well as a specific listing of clinical cases used in deriving these tables (Tables 6-7). Please note that Table 1 in the Attachment corresponds to Table 32 in the draft Advisory Committee Background Package that has been provided to the Agency under separate cover.

Although analyses of this type have limitations, these data demonstrate a consistent advantage in POB events with rofecoxib, compared with NSAIDs.