because of administrative or personal reasons, or represented a protocol mandated endoscopy for a non-GI related purpose.

Requested Analysis

As noted, we have reanalyzed the database after excluding the 14 cases identified by FDA (Table 1). The analytical procedures and display are the same as followed in Protocol 069, [Table 12, section II.C.3.a 1)].

The cumulative incidence of PUB was lower in the MK-0966 group (1.33%) than in the NSAID group (2.06%). The relative risk (MK-0966 vs NSAID) over the 12 month treatment period was 0.45 (95% CI 0.24, 0.85, p=0.01). This is similar to that observed in the original analysis.

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:\amirault\fda\101

Federal Express #1
Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Lawrence Goldkind, HFD-180, PKLN 6B45, Federal Express #2

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

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March 22, 1999

NDA ORIG AMENDMENT
BP

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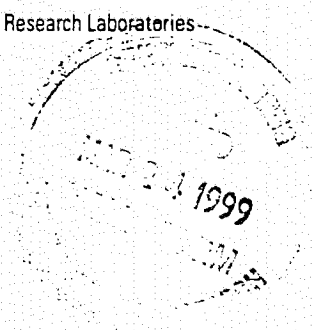

Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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 sent by Ms. Sandra Cook, (FDA) to Dr. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on March 16, 1999 with a request from the Pharmacology/Toxicology reviewer.

By this letter, MRL is providing a response to the Agency's request.

FDA Request: Please provide the values that you used to calculate exposure of the following animal studies to humans. What AUC value was used for 60 mg/kg/day for the second mouse carcinogenicity study and from what study was the AUC value obtained? What human AUC values are you using for the 25 mg and 50 mg doses? We want to verify that we are using the same values for labeling purposes.

Merck Response: The values used to calculate margins of exposure from animal studies to humans is detailed below. The human dosage used in the calculation was the 25 mg dose (the highest recommended dose for treatment of osteoarthritis). The AUC value for 25 mg in people was 3.87 μg•hr/ml (obtained from Protocol 043).

Plasma drug level determinations for mice were obtained in the 5-week Toxicokinetic Study (TT #95-611-0). Multiple dose plasma levels were determined at 30, 100, 300, 600 and 1000 mg/kg/day. Plasma drug levels were shown to be linear over the dose range of 30 to 600 mg/kg/day. Extrapolating from linear kinetics seen over the dose range (30 to 100 mg/kg/day), we estimated the exposure at 60 mg/kg/day (29.7 μg•hr/ml) determined the margin of safety at 60 mg/kg/day to be approximately 7-fold over the clinical dosage of 25 mg. It is important to note that the margin of exposure achieved when one compares the systemic exposure achieved in people at 12.5 mg and the systemic exposure

achieved at 30 mg/kg/day in mice determined in the 5-week toxicokinetic study is also approximately 7-fold.

The calculations of systemic exposure margins used for pregnant rats and rabbits were derived from the Oral Toxicokinetic Study in Pregnant Rats and Nonpregnant Rats (TT #95-709-0, -1, -2) and the Oral Toxicokinetic Study in Pregnant and Nonpregnant Rabbits (TT #95-722-0, -1).

In both rabbits and rats, no fetal malformations were observed at 50 mg/kg/day (the highest dose tested). Mean systemic exposure obtained in pregnant rats on gestation day 20 administered 50 mg/kg/day was 112.97 μg•hr/ml. This exposure is approximately 29 times the exposure noted in people at 25 mg (3.87 μg•hr/ml). In pregnant rabbits, systemic exposure was determined at 25 and 150 mg/kg/day. Systemic exposure at 50 mg/kg/day in rabbits (8.49 μg•hr/ml) was extrapolated from the systemic exposure at 25 and 150 mg/kg/day based on linear kinetics. Therefore, the margin of exposure achieved at 50 mg/kg/day was determined to be approximately 2-fold over that achieved in people at 25 mg.

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:\amirault\fda\103

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

Robert E. Silverman, M.D., Ph.D.
Senior Director
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March 22, 1999

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Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
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Food and Drug Administration
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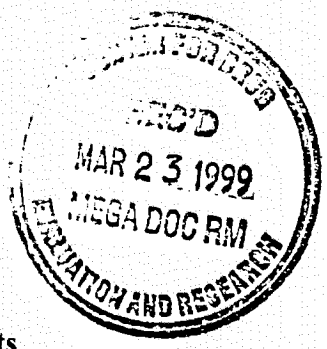
Rockville, MD 20857



Dear Dr. DeLap:

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

Reference is made to the above New Drug Application (NDA) and to an e-mail request to Dr. Robert Silverman, M.D., Ph.D., Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. from Ms. Sandra Cook (FDA) on March 15, 1999 with a request from the Pharmacology/Toxicology reviewer.

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

FDA Request: Please provide historical control data in the rat and rabbit for the incidence of fetal abnormalities for Segment II studies.

MRL Response: The historical control data for Fetal Alterations in Rats (Table 1) and Rabbits (Table 2) are provided. The tables provide the historical control incidence for all types of alterations seen in any group in the Segment II studies with VIOXX™.

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 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

q:\amirault\fda\102
Attachments

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

Robert E. Silverman, M.D., Ph.D.
Senior Director
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March 23, 1999

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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 request from the Agency on March 18, 1999; a submission from Merck Research Laboratories (MRL), on March 19, 1999; and a follow-up teleconference between Dr. Robert E. Silverman (MRL) and Dr. Goldkind (FDA) on March 22, 1999 during which the Agency requested another reanalysis of the PUB data from Protocol 069.

By this letter and attachment, MRL is providing a response to the Agency's request.

FDA Request: Please refer to the Agency's e-mail of March 18, which requested a re-analysis of protocol 069 after excluding 14 patients, and the response provided by MRL on March 19.

Please reanalyze the database for protocol 069 with the following changes to the FDA list of 14 patients: delete case #62 from the list of exclusions, and add case #32 to the list of exclusions. Please apply this revised list to confirmed cases, as well as confirmed plus unconfirmed cases.

MRL Response: The requested analyses are provided (Attachment Tables 1 and 2). The results are consistent with those in the original analysis. The relative risks for rofecoxib vs. NSAID over the 12-month treatment period were 0.51 and 0.41 for the two analyses.

Methodological comments

A number of methodological reservations were expressed in our previous response that still apply; these related to the decision to replace the adjudication's of the blinded Case

Review Committee with those of the Agency now that the treatments are unblinded and the analytical results are known.

We are unclear about the rationale for an additional aspect of the present request, specifically to analyze the subpopulation of patients that remains after excluding two types of cases: those that were not confirmed by the blinded case review committee *and* those that were excluded based on the FDA reviewer's evaluation. The two approaches reflect very different conditions of review,

and it seems more logical to apply them independently. Nonetheless, MRL has performed the requested reanalysis, per the Agency's new instructions.

Requested Analyses

The FDA's list of 14 cases for removal includes 12 that were confirmed by the Case Review Committee and 2 that were not.

In the first analysis, addressing the Agency's request to apply its exclusions to the set of confirmed cases, we began with 55 reported cases. Next, we excluded all 6 cases that were not confirmed by the Case review committee; two of these 6 cases were also excluded by FDA. Then we excluded the additional 12 cases identified by FDA, leaving a total of 37 cases. In this analysis (Table 1), rofecoxib remained significantly superior to NSAID, relative risk 0.51 (95% CI 0.26, 1.00; p=0.045).

In the second analysis, we began with 55 cases, and excluded the 14 cases identified by FDA, leaving a total of 41 cases. In this analysis (Table 2), rofecoxib remained significantly superior to NSAID, relative risk 0.41 (95% CI 0.22, 0.77; p=0.004).

In both cases, the results are consistent with the original analysis, i.e. have similar relative risk.

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:\amirault\fda\104

Attachment

Federal Express #1
Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Lawrence Goldkind, HFD-180, PKLN 6B45, Federal Express #1

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

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March 23, 1999

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Robert DeLap, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
CDER, ODE V HFD-550, Room 2063
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. DeLap:

NDA 21-042: VIOXX™ (Rofecoxib) Tablets
NDA 21-052: VIOXX™ (Rofecoxib) Oral Suspension

Safety Update Report

Reference is made to the above New Drug Applications (NDAs) submitted November 23, 1998. Submitted with this letter is a single Safety Update Report (SUR) for these NDAs. This SUR is being provided simultaneously in both paper copy and electronic format, with the exception of Item 11 (Case Report Tabulations) which is being provided in electronic format only.

This SUR provides updated safety information for rofecoxib subsequent to the original NDAs submitted on November 23, 1998. Throughout this report, safety data are reported in a variety of categories. Application data refer to the data as they were originally reported in the NDA. SUR data refer to data derived from patient visits that occurred during the SUR reporting period, April 1, 1998 to September 4, 1998. Cumulative data encompass both the Application and SUR data. As such, it is the most current reporting of the rofecoxib safety profile. Updated data refers to corrections to completed studies received after the Application cut-off date for an individual study.

The Application demonstrated that rofecoxib was generally safe and well tolerated in both OA and analgesia patients. Increases in the incidence of adverse experiences are expected in the Cumulative data due to the longer duration of treatment. However, the Cumulative safety data, when compared with the Application safety, are consistent with

the safety profile originally reported. There were no new clinically important adverse experiences with these longer durations of exposure.

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.

Please direct questions or need for additional information to 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

Federal Express #1

Desk copy: (cover letter + 4 copies with attachments) Ms. Sandra Cook, Project Mgr,
HFD 550, Room N-322
Federal Express #1

Q\robinson\defusco\surcover

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

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March 23, 1999

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

NDA ORIG AMENDMENT
BM

Dear Dr. DeLap:

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

Reference is made to the above New Drug Application (NDA) and to an e-mail sent to Dr. R. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. from Ms. S. Cook (FDA) on March 23, 1999 referring to a previous request from the GI Reviewer on March 11, 1999 and an MRL response on March 16, 1999.

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

FDA Comment 1: Please send an analysis of withdrawal due to NSAID-type adverse event by dose of VIOXX and individual NSAID for study 069. This analysis was done for the VIOXX groups combined compared to the NSAID group combined. This parameter was not included in your response on March 16th to our request of March 11th.

MRL Response: The requested information is provided in the Attachment. These analyses are consistent with the results provided previously in the original NDA. The attached tables are similar in format to the ones which were provided last week to address the first request. Our submission of March 16, 1999 explained the nature of the summary statistics contained in the tables; the caveats discussed in the previous response apply.

The data indicate that the incidence of discontinuation due to NSAID-type GI AE's was generally numerically less in the rofecoxib groups than in the NSAID comparator groups. Splitting the combined rofecoxib and combined NSAID groups, as requested, reduces the sample size in many of the cells. Therefore, the confidence limits overlap.

More specifically, the original analysis of Protocol 069 provided analyses of the incidence of discontinuation due to NSAID-type GI AE for the combined rofecoxib groups versus the combined NSAID groups (Table 33). That analysis showed a relative risk (RR) of 0.69 (95% CI 0.46, 1.03), which was similar to the RR for discontinuation due to any GI AE (0.70; 95% CI

0.52, 0.94; 069 CSR Table 32). The results in the attached tables for discontinuation due to NSAID-type GI AE's are consistent with the combined results for both of these end points.

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/ltr/634

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.
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215 652 5000

March 23, 1999

DESK COPY

MERCK
Research Laboratories

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, Maryland 20850

NDA 21-042: VIOXX™ Tablets
NDA 21-052: VIOXX™ Oral Suspension
(Rofecoxib)

SAFETY UPDATE REPORT

By copy of this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one (1) Compact Disk (CD) which contains the Safety Update Report (SUR) for NDA 21-042: VIOXX™ Tablets and NDA 21-052: VIOXX™ Oral Suspension (Rofecoxib), submitted in hardcopy to the Division of Anti-inflammatory, Analgesic & Ophthalmic Drug Products on March 23, 1999.

The information on the CD [redacted] is to be made available to the reviewers of the Division of Anti-inflammatory, Analgesic & Ophthalmic Drug Products.

A list of reviewers from the Division of Anti-inflammatory, Analgesic & Ophthalmic Drug Products who should be provided access to this electronic submission from their desktops may be obtained from Ms. Sandra Cook, Project Manager. MRL will follow up with Ms. Sandra Cook to ensure that the appropriate reviewers have been given access to this electronic review aid.

We have taken precautions to insure that any software on the CD is free of computer viruses and we authorize the use of anti-virus software, as appropriate.

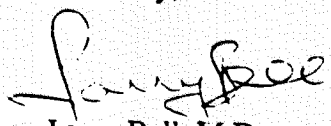
There are two attachments to this letter:

Attachment 1 A Table of Contents of the accompanying electronic submission.

Attachment 2 A complete list of file names.

During the time that the electronic review aid is actively being used, MRL will provide technical support. Any questions relating to this electronic submission should be addressed to me (610/397-2310) or, in my absence, Margo Herron (301/881-9000).

Sincerely,



Larry Bell, M.D.
Senior Director
Regulatory Affairs

Attachments

Enclosures: Compact Disk

Federal Express #1

Cc (cover letter only):
K. Edmunds, Division of Technology Support Services Staff, HFD-70
Federal Express #2

Ms. Sandra Cook, Project Manager, HFD-550, Room N-322,
Federal Express #3

cc (cover letter with attachments):
Central Document Room
NDA 21-042: VIOXX™ Tablets, HFD-550 (2 copies)
NDA 21-052: VIOXX™ Oral Suspension, HFD-550 (2 copies)
Federal Express #3

Q\robinson\defusco\vioxx_cd

Robert E. Silverman, M.D., Ph.D.
Senior Director
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March 23, 1999

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

NDA ORIG AMENDMENT
BS

Dear Dr. DeLap:

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

Reference is made to the above New Drug Application (NDA); a March 16, 1999 submission of a response to an FDA request on March 11, 1999 and a follow-up teleconference on March 22, 1999, during which Dr. Li (FDA) requested additional information related to the statistical analysis of confirmed PUBs in Protocol 069.

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

FDA Comment: Please provide the SAS output which supports the tables provided in the March 16 submission on pages 19 and 20. In addition, please provide the results of the analyses in pages 19 and 20 as survival plots, particularly with regard to the rofecoxib 50 mg and ibuprofen treatment groups.

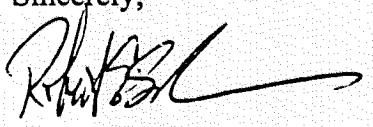
MRL Response: The requested information is provided in the attachments. The SAS output (Attachment 1) is provided for the analyses of each treatment group in the tables on pages 19 and 20 of the March 16 submission. A survival plot with all treatment groups, as well as a survival plot with just the rofecoxib 50 mg and ibuprofen groups, are provided in Attachment 2.

As shown in the attached output, the sample size in the ibuprofen group depletes to 7 patients at Day 176, the time of the last ibuprofen PUB event. As noted in the MRL submission of March 16, the estimates at the later time points needed to be interpreted with caution because of small sample sizes at the completion periods of the respective studies. In the 50 mg group, the sample size was 360 patients at the time of the last event within the first 6 months, and 94 patients at six months.

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/ltr/635

Attachment

Federal Express #1

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