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/640

Attachment

Federal Express #1

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Susan Wilson, HFD-550, CRP2 N368, Federal Express #1

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

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

ORIGINAL

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MERCK
Research Laboratories

April 1, 1999

NC
1

Robert J. DeLap, M.D., Ph.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 a fax sent by Ms. Vickey Lutwak, (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. on April 1, 1999; and a follow-up telephone conversation between Ms. Lutwak and Dr. Silverman on April 1, 1999.

By this letter MRL is providing a response to the Agency's fax of April 1, 1999.

FDA Comment: Please send the following original material to the medical reviewer in electronic format. Please let me know at what date we can expect this material; we are eager to get it.

Please ask Merck to provide scanned copies of the original CRFs (case report forms) for Deaths and Dropouts due to adverse experiences.

MRL Response: "Original" CRFs for the clinical studies in this NDA were compiled by direct electronic entry of information at the investigative sites (i.e. remote data entry). Therefore, the CRFs provided electronically in Item 12 of the NDA for patients who died or discontinued due to an adverse event are copies of the "original" CRFs as they exist at the sites for these patients.

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\109

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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DUPLICATE

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April 5, 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

Dear Dr. DeLap:

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

Reference is made to the above New Drug Application (NDA) and a telefax from Ms. Lutwak (FDA) to Dr. R. Silverman, Merck Research laboratories (MRL), a Division of Merck & Company, Inc on March 31, 1999 with a request from the Medical Reviewer.

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

FDA Comment 1: Could you please ask Merck to direct me to or to provide a narrative and CRF of the patient with elevated amylase and lipase in study 058?

MRL Response: The patient with elevated lipase and amylase in Protocol 058 is AN 1436. A brief narrative for this patient exists in the Clinical Study Report for this protocol (NDA 21-042; Clinical Documentation; Reference P058; page 119). This patient's case report form is provided electronically in the NDA (Case Report Form; Discontinuations due to AE; 058-052; 1436). This patient was admitted to the hospital for a complaint of chest pain. Additional information on the laboratory tests not contained in the existing narrative is provided.

The patient had mildly elevated serum lipase and amylase levels (53 IU/dL and 152 U/L) upon admission, Study Day 7. These elevations were considered incidental lab findings only. On Study Day 19, 13 days after the last dose of study therapy (therapy was discontinued on Study Day 6 for reasons unrelated to the lipase/amylase elevations) serum lipase and amylase levels were normal (124 U/L and 57 U/L). The adverse experiences of elevated lipase and amylase were considered not related to study therapy by the investigator.

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/642

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

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MERCK
Research Laboratories

April 6, 1999

NDA ORIG AMENDMENT
BM

Robert J. DeLap, M.D., Ph.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 a fax sent by Ms. Vickey Lutwak, (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. on April 5, 1999 containing two requests from the GI reviewer; and a follow-up telephone conversation between Dr. Silverman and Dr. Goldkind on April 5, 1999.

By this letter MRL is providing a response to the Agency's fax of April 1, 1999.

FDA Request 1: Please ask Merck to site the reference for the esophageal scorning system that was in their endoscopic studies.

MRL Response 1: In the osteoarthritis endoscopy studies (Protocols 044/045), the Hetzel-Dent esophageal grading scale was used during protocol endoscopies, as referenced in Appendix 3.2.1 of the Protocol 044 and 045 clinical study reports (Attachment 1: Hetzel DJ, Dent J, Reed WD et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology 1988; 95:9003-12.).

Please note that during upper endoscopies other than those performed by Protocol 044/045 investigators, other esophageal grading scales may have been used. In particular, PUB Case number 62 (discussed previously with the GI reviewer, an investigator in Protocol 034 applied the Savary-Miller esophageal grading scale, commonly used outside the U.S. (Attachment 2: Savary M and Miller G: The Esophagus. Handbook and Atlas of Endoscopy. Geneva, Gassmann AG, 1978, 135.).

FDA Request 2: Please ask to have the endoscopy reports from non-English speaking sources in the original language translated. This documentation is needed before final review.

MRL Response 2: As discussed with Dr. Goldkind, the previously requested documents from English speaking sites will be forwarded as soon as they are available within the next few weeks. The documents that require translation will require extra time and will be forwarded subsequently when the translations are completed.

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\110

Attachments (2)

Federal Express #1

Desk Copy:

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

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

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April 12, 1999

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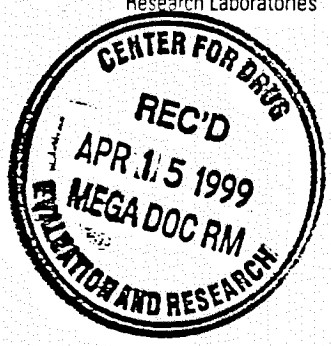

Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. DeLap:

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

Reference is made to the above New Drug Application, the forthcoming Arthritis Advisory Committee Meeting (AACM) on April 20, 1998, and a pre-AACM meeting held between the FDA and representatives of Merck Research Laboratories (MRL), a division of Merck & Company, Inc. on April 8, 1999. During the meeting, MRL agreed to provide the Agency with an analysis of "responding" patients from the dental pain studies to support the duration of analgesic effect.

By this letter and attachment, MRL is providing this response.

Merck Response:

Three complimentary analyses were performed in those patients who demonstrated an initial analgesic response (i.e., exclusion of "non-responders") to assess the time to re-medication in the dental pain studies (Protocols #066 and #071). To assess the duration of analgesia effect, each of these analyses was performed on one of the following restricted subsets of patients:

- patients who did not take rescue medication within 2 hours of treatment administration;
- patients who experienced confirmed perceptible pain relief (i.e. stopwatch time of perceptible pain relief, confirmed by the second stopwatch);
- and patients who experienced PID $\geq$ 1.

Treatment effects on the time to re-medication were assessed using the Cox proportional hazards regression model. The model included treatment and baseline Pain Intensity (PI) score as factors. The treatment-by-baseline PI score was tested using the likelihood-ratio statistic. The interaction term was removed from the model if it was found not significant

at the 5% level. Treatment effects and between-group comparisons were assessed by evaluating the risk ratio (with 95% CI) of the hazards function for each active treatment versus placebo and between pairs of active treatments. Contrasts obtained from the model were used for between-treatment pair-wise comparisons. Treatment effects were also evaluated by comparing, between treatments, the Kaplan-Meier product limit estimates of the 25th, 50th , and 75th percentiles. The 95% CI for the 50th percentile (i.e. when 50% of the patients re-medicated) is provided. A nonparametric analysis using the log-rank test was also performed. Results from the Cox proportional hazards regression analysis, the nonparametric log-rank test, and the summary statistics of the time to re-medication by percentile are presented in Attachment 1.

The results support the conclusion that rofecoxib 50 mg maintains analgesic efficacy for 24 hours in those patients who initially responded.

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\111

Attachment

Federal Express #1
Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Mordechai Averbach, HFD-550, CRP2 N320, Federal Express #2

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

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April 13, 1999

MERCK
Research Laboratories

Robert J. DeLap, M.D., Ph.D. Acting Director
Division of Anti-Inflammatory, Analgesic and
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Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20857

ORIG AMENDMENT
BP

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 16 1999
MEGA DOC RM

Dear Dr. DeLap:

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

Reference is made to the above New Drug Application, the forthcoming Arthritis Advisory Committee Meeting (AACM) on April 20, 1998, and a pre-AACM meeting held between the FDA and representatives of Merck Research Laboratories (MRL), a division of Merck & Company, Inc. on April 8, 1999. During this meeting, the reviewing pharmacologist requested additional information/clarification.

By this letter and attachments, MRL is providing responses to these requests.

FDA Request 1: Could the sponsor please provide a table on the in vitro COX-1 and COX-2 activity of rofecoxib and the metabolites.

Merck Response 1: Table 1 provides the results of the in vitro human whole blood assay demonstrating the COX-1 (IC_{50}) and COX-2 (IC_{50}) activity for rofecoxib and metabolites.

FDA Request 2: Please provide urinary metabolite data (dihydrohydroxy acid metabolites) of rofecoxib in mice.

Merck Response 2: Table 2 provides the data for the urinary dihydrohydroxy acid metabolite profile of rofecoxib in the mouse, rat, dog and human.

FDA Request 3: The Agency has requested clarification on the nature of the vertebral malformations noted in the Oral Developmental Toxicity Study in Rabbits (TT #95-704-0).

Merck Response 3: The incidence and nature of the vertebral malformations are presented in Table 3. A total of five fetuses in the 50 mg/kg/day group were identified with vertebral malformations. One of the five fetuses in the 50 mg/kg/day group with vertebral malformation had a missing vertebrae (thoracic and lumbar vertebral count of 18). A missing vertebra was also noted in a fetus in the concurrent control group and, therefore, this change is not related to treatment.

Of the four remaining fetuses in the 50 mg/kg/day group with vertebral malformations, two fetuses were from the same litter (Dam #95-0061) of only two fetuses, both which had multiple external and visceral malformations (both with shortened tails and one also had omphalocele and fused kidneys). These findings are considered to be an individual litter variation since a similar combination of fetal findings were not noted in the other 17 litters in this group and the spectrum of alterations has no common embryological relationship.

Based on these considerations and exclusion of these fetuses from the fetal skeletal analysis, the total number of fetuses in the 50 mg/kg/day group with only vertebral malformations is 2 (fetal incidence of 1.42%), which is within the historical control range for vertebral malformations (cervical, thoracic, lumbar) for this lab (0-1.97%). Alternatively, inclusion of the two fetuses from the same litter with multiple malformations and including the total incidence of vertebral malformations across all groups, the number of fetuses with vertebral malformations would be 0, 2. 2, and 4 fetuses in the control, 10, 25, and 50 mg/kg/day groups (incidence rate of 0, 1.47%, 1.59% and 2.84%, respectively). However, the spectrum of vertebral malformations is different for each fetus and when broken down by incidence, according to region and description (see attached), all values are within the MARTA (Mid-Atlantic Regional Teratology Association) historical control range (ref. 1). The MARTA historical control range of vertebral malformations for related alterations is a follows: Cervical (including bipartite, fused, misaligned or misshapen) is 0-1.96%, Thoracic (including agenesis, bipartite, fused, hemicentra, hypoplastic or misshapen) is 0-2.65% and Lumbar (including bipartite or fused) is 0-2.63%. Therefore, based on the nature of the vertebral malformations and the incidence within historical control range, the vertebral malformations noted in the Oral Developmental Toxicity Study in Rabbits is not considered related to treatment.

FDA Request 4: Could MRL provide references on the use of examining the number of ossified sacrocaudal vertebrae vs. an overall indicator of fetal ossification.

Merck Response 4: Attached are a series of references on the evaluation of ossification in rats, mice and rabbits. The most detailed discussions on the use of sacrocaudal vertebral ossification as an overall indicator of fetal ossification is in the papers by Fumio Ariyuki et al. (1980 and 1982). In these papers, he showed a linear relationship between body weight (age) and the number of ossified sacrococcygeal vertebra. Unlike ossification of the other structures, the distribution of ossified sacrocaudal vertebra was normal (gausian), making it the most reliable parameter relative to ossified sternebra or phalanges, which had a curvilinear relationship to body weight. These studies were done in rats but there is no reason to believe that the rabbit is different in the development process. One paper (Hans Fritz, 1974) discusses the relationship of ossification and fetal weight in rabbits. In addition, several papers referenced in that publication from the 60's and 70's refer to ossification of the axial skeleton as an overall indicator of overall fetal ossification.

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\113

Attachment

Federal Express #1
Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Susan Wilson, HFD-550, CRP2 N368, Federal Express #2

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April 15, 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
9201 Corporate Boulevard
Rockville, MD 20850

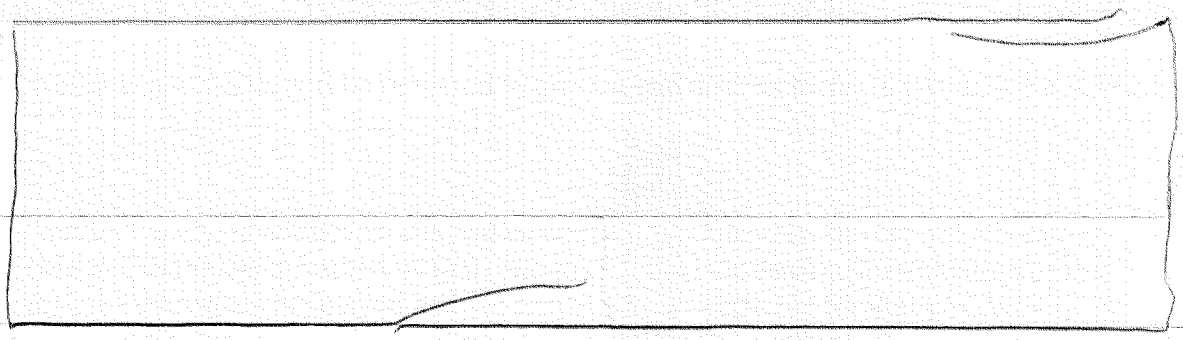
Dear Dr. DeLap:

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

Reference is made to the above New Drug Application; the forthcoming Arthritis Advisory Committee Meeting (AACM) on April 20, 1999; a pre-AACM meeting between representatives of FDA and Merck Research Laboratories (MRL), a Division of Merck & Company, Inc., on April 8, 1999; and a telephone conversation between Dr. Pelayo (FDA) and Dr. Silverman (MRL) on April 12, 1999. During the April 8 meeting and April 12 conversation, Dr. Pelayo made several requests for additional information. By this letter and attachments, MRL is providing a response to these requests.

FDA Comment 1: Please provide an

FDA Comment 2: The NDA does not contain data



FDA Comment 3: Please provide an analysis of discontinuations due to the adverse experiences of hypertension and edema for the following Protocol groups: Protocols 034/035, first 6 months; Protocols 044/045, placebo controlled period (4 months); and Protocol 058.

MRL Response: Attachment 3 provides tabular presentations of the requested information.

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/643

Attachment

Federal Express #1

Desk Copy: Dr. Juan Pelayo, HFD-110, WOC2 5073, Federal Express #2

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

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April 15, 1999

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

MERCK
Research Laboratories

ORIGINAL
NC

Dear Dr. DeLap:

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

Reference is made to the above New Drug Application (NDA) submitted November 23, 1998; a teleconference between Merck Research Laboratories (MRL) and the FDA on March 22, 1999; and a follow-up conversation on March 26, 1999 whereby Dr. Goldkind (FDA) requested copies of source documentation of the endoscopists reports.

FDA Request: Please provide copies of the endoscopists reports from the following sites in Protocols 044 and 045:

Protocol 044: 4, 6, 19, 24, 32, 33
Protocol 045: 9, 10, 18, 20, 21, 30

MRL Response: Attached please find Case Report Forms and endoscopy notes for the following investigators:

Dr. Genta	044-004
Dr. Johanson	044-006
Dr. Shah	044-019
Dr. Zizic	044-024
Dr. Schwartz	044-032
Dr. Stern	044-033
Dr. Graham	045-018
Dr. Cello	045-030

In the process of assembling this request, it has come to our attention that some documents were missing. See attachment 1 for more details.

Information from the following sites (all non-U.S.) will be forthcoming when we receive them. Some require translations to English.

Protocol 045: 9, 10, 20, 21