CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-042/S-007, S-008, S-010, S-012, S-013, S-014 and 21-052/S-004, S-005, S-006, S-007, S-008, S-009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-042/S-007, S-008, S-010, S-012, S-013, S-014
NDA 21-052/S-004, S-005, S-006, S-007, S-008, S-009

Merck & Co., Inc.
Ned Braunstein, M.D.,
Director, Regulatory Affairs
P.O. Box 2000
RY 33-720
Rahway, NJ 07065

Dear Dr. Silverman:

Please refer to your supplemental new drug applications:

NDA 21-042/S-007 dated June 29, 2000 received June 29, 2000;
S-008 dated July 10, 2000, received July 11, 2000;
S-010 dated September 29, 2000, received October 02, 2000;
S-012 dated February 28, 2001 received March 01, 2001;
S-013 dated April 05, 2001, received April 05, 2001, and
S-014 dated October 02, 2001, received October 03; 2001;

NDA 21-052/S-004 dated June 29, 2000 received June 29, 2000;
S-005 dated July 10, 2000, received July 11, 2000;
S-006 dated September 29, 2000, received October 02, 2000;
S-007 dated February 28, 2001 received March 01, 2001;
S-008 dated April 05, 2001, received April 05, 2001, and
S-009 dated October 02, 2001, received October 03; 2001,

submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vioxx (rofecoxib tablets) Tablets 12.5 mg, 25 mg, 50 mg and Vioxx (rofecoxib suspension) Suspension 12.5 mg/5 mL, 25 mg/5 mL, respectively.

We acknowledge receipt of your submissions for NDA 21-042/S-007 dated October 6, 13, and 27; November 13; December 5, 6, 18, 20 (2), and 21, 2000; January 12 (2), 13 (2), 15, 17, 19 (3), 20, 23, 25 (2), 29, and 30 (3); February 1, 2 (2), 5, 6, 7, 15, 16 (2) 21, 23, 27 (2), and 28; March 2, 8, 13, 15 (2), 16, 22, and 30; April 13, 16, and 30; May 16, 21, and 25; June 12, 14, 19, 22, and 29; July 9, 12, 26, 27, and 30; August 3, and 17; October 1, 3, 5, and 8; November 5, 6, 9, 16, and 26; December 5 (2), and 18, 2001; January 7, 17, and 21; February 5, 19 (2), and 25; March 5, 21 (2), 22, and 29; April 2, and 3, 2002 .

We acknowledge receipt of your submissions for NDA 21-042/S-012 dated March 23; April 30; May 04, and 16; June 22, 27 (2); July 20, and 27; August 13; September 20, and 21; October 11; November 09, December 5, and 21, 2001; and April 3, 2002.

We acknowledge receipt of your submissions for NDA 21-052/S-004 dated October 6, and 13; March 2, and 21; April 13; May 21; October 11; November 06; December 05, 2001; January 7, 17, and 21; February 5, and 19; March 21; and April 3, 2002.

We acknowledge receipt of your submissions for NDA 21-052/S-007 dated March 23; June 27, 2001; January 4; and April 3, 2002.

Your submission of April 03, 2002 constituted a complete response to our January 11, 2002 action letter.

These supplemental new drug applications provide for the use of Vioxx (rofecoxib) Tablets 12.5 mg, 25 mg, Vioxx (rofecoxib) Suspension 12.5 mg/5 mL, 25 mg/5 mL:

NDA 21-042/S-007 and NDA 21-052/S-004 provide for proposed labeling changes in the Clinical Pharmacology, Clinical Studies, Warnings, Precautions, and Adverse Reactions sections;
NDA 21-042/S-008 and NDA 21-052/S-005 provide for changes in the Clinical Pharmacology and Precautions section to include pharmacokinetic data in patients with moderate hepatic insufficiency, drug interaction with theophylline, drug interaction with methotrexate;
NDA 21-042/S-010 and NDA 21-052/S-006 provide for inclusion of post-marketing adverse reactions and post-marketing experience of concurrent administration of clinical doses of Vioxx with lithium;
NDA 21-042/S-012 and NDA 21-052/S-007 provide for indication of rheumatoid arthritis;
NDA 21-042/S-013 and NDA 21-052/S-008 provide for post-marketing adverse reactions and post-marketing experience of hypersensitivity vasculitis and hyperkalemia; and
NDA 21-42/S-014 and NDA 21-052/S-009 provide for post-marketing adverse reactions and post-marketing experience of hepatic failure, bronchosopasm, toxic epidermal necrolysis, and analphylactic reaction.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 21-042/S-007, S-008, S-010, S-012, S-013, S-014, 21-052/S-004, S-005, S-006, S-007, S-008, S-009." Approval of these submissions by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or

601.27); however we acknowledge your Pediatric Written Request issued on December 06, 2001 for pediatric studies to be submitted on or before December 31, 2003.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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 Division Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

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
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ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-042/S-007, S-008, S-010, S-012, S-013, S-014 and 21-052/S-004, S-005, S-006, S-007, S-008, S-009

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21042/S-012
NDA 21052/S-007

Merck Research Laboratories
Attention: Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs
Sumneytown Pike
P.O. Box 4,BLA-20
West Point, PA 19486-0004

Dear Dr. Silverman:

Please refer to your supplemental new drug applications dated February 28, 2001, received March 01, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vioxx™ (rofecoxib) tablet 12.5 mg and 25 mg, Vioxx™ (rofecoxib) Suspension 12.5/5 mL and 25 mg/5 mL.

We acknowledge receipt of your submissions dated March 23, April 30, May 04, May 16, June 22, June 27 (2), July 20, July 27, August 13, September 20, September 21, October 11, November 09, December 05, 2001.

These supplemental new drug applications propose for the use of Vioxx™ (rofecoxib) tablet 12.5 mg and 25 mg, Vioxx™ (rofecoxib) Suspension 12.5/5 mL and 25 mg/5 mL for the indication of rheumatoid arthritis.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit revised draft labeling.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically (to each application) according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL (to each application), ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDAs by submitting all safety information you now have regarding your new drugs. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with **this/these** change(s) prior to approval of these supplemental applications.

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 Division Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products
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
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APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-042/S-007
NDA 21-052/S-004

Merck & Co., Inc.
Attention: Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, Pennsylvania 19486

Dear Dr. Silverman:

Please refer to your supplemental new drug applications dated June 29, 2000, received June 29, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vioxx (rofecoxib tablets) Tablets, 12. 5 mg, 25 mg, and 50 mg, and Vioxx (rofecoxib suspension) Suspension, 12.5 mg/5 mL and 25 mg/5 mL.

We acknowledge receipt of your submissions for NDA 21-042/S-007 dated August 7; October 6, 13 and 27; November 13; December 5, 6, 18, 20 (2) and 21, 2000; January 12 (2), 13, 15, 17, 19(3), 20, 23, 25 (2), 29, and 30 (3); February 1, 2 (2), 5 (2), 6, 7, 15, 16 (2), 21, 23, 27 (2) and 28; and March 2, 8, 13, 15 (2), 16, 21, and 22, 2001.

We acknowledge receipt of your submissions for NDA 21-052/S-004 dated August 7; October 6, 13 and 27; November 13, 2000; and March 2 and 21, 2001.

These supplemental new drug applications propose labeling changes in the Clinical Pharmacology, Clinical Studies, Warnings, Precautions, and Adverse Events sections, as a result of a gastrointestinal outcome study for Vioxx.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to address the following:

> We consider a full and complete review of all relevant data essential to the safety evaluation for these supplements. Therefore, we consider review of the ADVANTAGE trial (study 102), necessary in order to adequately interpret the cardiovascular and overall safety results in the VIGOR study and to provide adequate labeling information. Please submit the complete study report for the ADVANTAGE trial (study 102), including the case report tabulations and the case report forms, for our review. We acknowledge receipt on March 30, 2001, of a partial response to this request. Please refer to previous information requests of November 27, 2000, and February 28, 2001.

In addition, all previous revisions as reflected in the most recently approved labeling must be included.

To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDAs by submitting all safety information you now have regarding your new drugs. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a re-tabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment

nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Sandra N. Folkendt, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Jonca Bull, M.D.
Acting Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Jonca Bull
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