CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-647

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 21-647

Patent Information

Item 13

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1. Active Ingredient	Rofecoxib
2. Dosage(s)	25 mg and 50 mg
3. Trade Name	VIOXX®
4. Dosage Form	Tablet
Route of Administration	Oral
5. Applicant Firm Name	Merck Research Laboratories
6. NDA Number	21-647
7. Approval Date	
8. Exclusivity	Three (3) years from this NDA Approval Date
9. Applicable Patent Numbers	U.S. No. 6,239,173 Expiration Date: June 24, 2013 U.S. No. 5,474,995 Expiration Date: June 24, 2013 U.S. No. 5,691,374 Expiration Date: May 18, 2015 U.S. No. 6,063,811 Expiration Date: May 6, 2017

A. This section should be completed for each individual patent

U.S. Patent Number: 5,474,995

Expiration Date: 6/24/2013

Type of Patent - indicate all that apply:

1. Drug Substance (Active Ingredient) ✓ Y__ N
2. Drug Product (Composition/Formulation) ✓ Y__ N
3. Method of Use ✓ Y__ N

Name of Patent Owner: Merck Frosst Canada & Co., Kirkland, Quebec, CANADA

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if the above listed patent has Composition/ Formulation or Method of Use claims.

The undersigned declares that United States Patent Number 5,474,995

covers the composition, formulation and/or method of use of VIOXX®

(name of drug product). This product is:

- ✓ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

and

- ✓ the subject of this application for which approval is being sought.

A. This section should be completed for each individual patent

U.S. Patent Number: 6,063,811

Expiration Date: 5/6/2017

Type of Patent - indicate all that apply:

1. Drug Substance (Active Ingredient) __ Y ✓ N
2. Drug Product (Composition/Formulation) __ Y ✓ N
3. Method of Use ✓ Y __ N

Name of Patent Owner: Merck & Co., Inc., Rahway, NJ/ Merck Frosst Canada & Co., Kirkland, Quebec, CANADA

U.S. Agent (If patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if the above listed patent has Composition/ Formulation or Method of Use claims.

The undersigned declares that United States Patent Number 6,063,811

covers the composition, formulation and/or method of use of VIOXX®

(name of drug product). This product is:

- ✓ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

and

- ✓ the subject of this application for which approval is being sought.

DRAFT

EXCLUSIVITY SUMMARY for NDA # 21-647 SUPPL #

Trade Name Vioxx **Generic Name** Rofecoxib

Applicant Name Merck **HFD-120**

Approval Date ****3/26/04*****

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_x_/

   b) Is it an effectiveness supplement? YES /_x_/ NO /___/

      If yes, what type(SE1, SE2, etc.)?
      Type 6 NDA for new indication (migraine)

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_x_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_x_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
Three (3) years from NDA approval date

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_x_/ NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_x_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /x_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_x_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-042 Vioxx (rofecoxib) tablets

NDA # 21-052 Vioxx (rofecoxib) oral suspension

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_x_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_x_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_x_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_x_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_x_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 161

Investigation #2, Study # 162

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_x_/
Investigation #2	YES /___/	NO /_x_/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /__x__/

Investigation #2 YES /___/ NO /__x__/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__1__, Study # __161__

Investigation #__2__, Study # __162__

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 61,419 010) YES /_x_/ NO /___/ Explain:

Investigation #2

IND # 61,419 010) YES /_x_/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD-120/Division File
HFD-120/Lana Chen
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-647 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: May 27, 2003 **Action Date:** March 26, 2004

HFD -120 **Trade and generic names/dosage form:** Vioxx (rofecoxib) tablets

Applicant: Merck **Therapeutic Class:** 6S

Indication(s) previously approved:

For relief of the signs and symptoms of osteoarthritis.
For the management of acute pain.
For the treatment of primary dysmenorrhea.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Migraine

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ✓ No: Please check all that apply: ✓ Partial Waiver ✓ Deferred ____ Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.**	**yr.** 0	**Tanner Stage**	
Max	**kg**	**mo.**	**yr.** 11	**Tanner Stage**	

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ✓ Too few children with disease to study
- ☐ There are safety concerns

- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Adolescents 12-17 years old

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ✓ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): 3/31/07

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Russell Katz
4/8/04 11:57:06 AM

MEMORANDUM

DATE: March 25, 2004

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-647

SUBJECT: Action Memo for NDA 21-647, for the use of Vioxx (rofecoxib) in the acute treatment of migraine

NDA 21-647, for the use of Vioxx (rofecoxib), a non-steroidal anti-inflammatory (NSAID) COX-2 inhibitor, in the acute treatment of migraine, was submitted by Merck Laboratories on 5/23/03. Vioxx is currently approved for the treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA), as well as for the management of acute pain and primary dysmenorrhea. This application contains the results of 2 randomized, single dose, controlled trials in patients with acute migraine, as well as a 3 month extension of one of the controlled trials, and a 3 month study of migraine prophylaxis. In addition, the sponsor presents chronic safety data in patients with OA and RA in support of the chronic safety in patients with migraine.

The application has been reviewed by Dr. Kevin Prohaska, medical officer (review dated 3/4/04), Dr. Sharon Yan, statistician (review dated 3/4/04), Dr. Martha Heimann, chemist (review dated 2/3/04), Dr. Andrea Powell, pharmacologist (review dated 3/8/04), Dr. Ni Khin, Division of Scientific Investigations (review dated 1/14/04), Ms. Jeanine Best, Division of Surveillance, Research, and Communication Support (review dated 2/25/04), Dr. Sharon Hertz, Division of Anti-inflammatory, Analgesic, and Ophthalmologic Drug Products (review dated 3/19/04), and Dr. Eric Bastings, Neurology Drugs Team Leader (memo dated 3/22/04). The review team recommends that the application be approved. I will briefly review the relevant safety and effectiveness data, and offer the rationale for the Division's action.

Efficacy

As noted above, the sponsor has submitted the results of 2 single dose randomized controlled trials in patients with moderate to severe migraine headaches (Studies 161 and 162). In each study, patients were randomized to a single dose of either Vioxx 25 mg, 50 mg, or placebo. The studies were of standard design. As the review team notes, the studies demonstrated statistically significant drug-placebo differences on pain as well as on the three associated symptoms (nausea, photophobia, phonophobia) at 2 hours, the primary time point of interest, except for the 2 hour Nausea rating in one study, Study 161, for the 25 mg group (p=0.1). In general, responses at the 50 mg

group were slightly numerically superior to those in the 25 mg group, although no between-dose comparison approached statistical significance.

Safety

In addition to the safety data from the acute single dose controlled trials, the sponsor submitted data from a 3 month study in which patients treated up to 8 acute headaches/month (this trial randomized patients to Vioxx 25 mg, 50 mg, or ibuprofen and was an extension of Study 162), as well as data from a 3 month study in which patients were randomized to a daily single dose of Vioxx 25 mg, montelukast, or placebo. In the 3 month extension to Study 162, the average number of headaches treated per month was about 3, with few patients treating more than 5 headaches/month.

Drs. Prohaska and Bastings described the safety data. In the acute single dose controlled trials, 377 patients received 25 mg and 388 patients received 50 mg. In the 3 month extension study, 268 patients received 25 mg and 244 received 50 mg. In the 3 month prophylaxis study, 89 patients were treated with 25 mg. In addition, as noted above, the sponsor submitted chronic data from patients with OA and RA (which examined doses up to 50 mg/day), and argues that these data should support the chronic safety of Vioxx as a treatment for acute migraine, primarily because 1) the safety profile of 25 and 50 mg single doses in the migraine population is similar to that seen in the primary dysmenorrhea studies (in which patients were treated with single doses of 50 mg, and which is approved for up to 5 days of dosing/month), and no new ADRs were seen compared to the OA and RA experience, 2) the migraine population is similar to the acute pain and dysmenorrhea populations, and the Agency previously accepted the chronic OA and RA data to support the chronic safety of Vioxx in acute pain and primary dysmenorrhea, and 3) the acute treatment of migraine entails intermittent treatment which would be expected to be safer than daily doses of 12.5 mg or 25 mg, as demonstrated in the OA and RA populations.

No unexpected ADRs were seen in the migraine safety database, although it is of some concern that in the 3 month prophylaxis study (in which patients received daily doses of 25 mg), there was a 3.4% incidence of CV ADRs compared to 0% in the placebo group.

Comments

The sponsor has submitted the results of two adequate and well-controlled studies that demonstrate the effectiveness of Vioxx 25 mg and 50 mg in the treatment of acute migraine headaches. The safety experience obtained in the migraine population poses no bar to approval.

However, as noted above, the sponsor has not provided chronic safety data in the migraine population of the sort usually required (typically, the division expects

that, for a new chemical entity proposed as a treatment for acute migraine, data from at least 300 patients who have treated at least 2 headaches/month and 100 patients who have treated at least 2 headaches/month, must be provided). In this application, the sponsor asserts that the long term experience at 12.5 and 25 mg/day in OA and RA patients should substitute for the typical long term safety data in migraine patients.

However, the experience in patients with OA and RA, while obviously acceptable in those populations, might be considered unacceptable for a treatment for migraine, especially at a dose of 50 mg/day given chronically, based on the relatively high rate of cardiovascular risk seen in the OA and RA populations at a daily dose of 50 mg. However, it is also clear that the Agency has previously approved the use of 50 mg/day for up to 5 days/month in a population relatively similar (women with primary dysmenorrhea) to that of the migraine population, and the sponsor has provided at least some data (up to three months) in patients who treated up to 8 headaches/month (although, as noted above, very few treated more than 5 headaches/month). For these reasons, I believe that the drug can be used safely in the treatment of acute migraine headache if labeling states that the safety of treating more than 5 headaches/month has not been established, and the recommended dose is 25 mg/day (although labeling should note that 50 mg/day can be given if necessary).

For the reasons given above, then, I will issue an Approval letter, with the attached labeling to which the sponsor and we have agreed.

Russell Katz, M.D.

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

/s/

Russell Katz
3/26/04 08:36:10 AM
MEDICAL OFFICER

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMOLOGIC DRUG PRODUCTS
HFD-550, 9201 Corporate Blvd, Rockville MD 20850 Tel:(301)827-2040

MEMORANDUM

DATE: March 17, 2004

TO: Russell Katz, M.D., Division Director, DNDP, CDER (HFD-120)

THROUGH: Brian Harvey, M.D. Ph.D., Acting Director, DAAODP, CDER (HFD-550)

FROM: Sharon Hertz, M.D., Deputy Director, DAAODP

RE: Consult re: VIOXX PI and PPI for Migraine

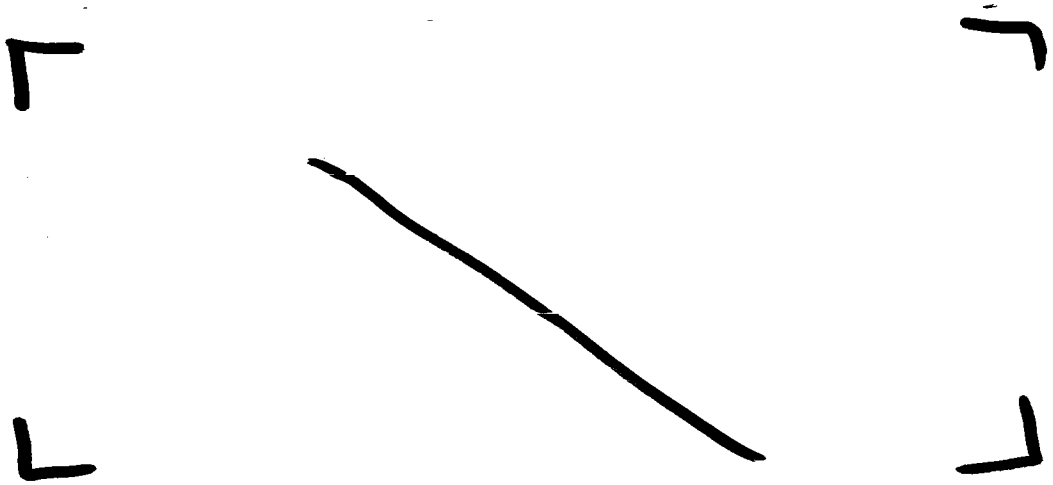
Findings:
I concur with the proposed changes to the Package Insert. I concur with most of the proposed changes to the Patient Package Insert, with the exception of the paragraph incorporating additional side effects as described below. This paragraph reports uncommon adverse events, some of which are already presented as serious side effects, and uses some terminology that is unsuitable for a lay person. I suggest adding "COX-2 selective" to the definition of VIOXX as a nonsteroidal anti-inflammatory drug.

Background:
The Division of Neuropharmacologic Drug Products has reviewed an efficacy supplement for the use of VIOXX in the treatment of migraine headache with or without aura. This Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products has been consulted for comments regarding the package insert (PI) and patient package insert (PPI).

The package insert reviewed for this consult included edits by DNDP. The additions by DNDP are all directly referable to the new indication. There is no conflict with any of the information pertaining to the original indications. No changes are suggested.

The PPI reviewed for this consult included edits by the Division of Drug Marketing, Advertising, and Communication (DDMAC), the Office of Drug Safety (ODS), and DNDP. The DDMAC and ODS edits were extensive and created a PPI with the format of a medication guide and content PPI comparable to recent PPIs for other NSAIDs and COX-2 inhibitors. The changes in content referable to the addition of the new migraine indication are clear and do not impact the existing information from the osteoarthritis, rheumatoid arthritis, acute pain, and dysmenorrhea indications. A list of the most serious and life-threatening side effects are provided under the heading "What is the most important information I should know about VIOXX?". There are also serious side effects

and the more common side effects under the heading, "What are the possible side effects of VIOXX?".



I suggest adding "COX-2 selective" to the definition of VIOXX as a nonsteroidal anti-inflammatory drug.

The PPI **with my edits along with the edits by DDMAC, ODS, and DNDP is presented below in Attachment 1.**

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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Chen, Lana Y

From: Bastings, Eric
Sent: Friday, March 12, 2004 12:11
To: Chen, Lana Y
Cc: Katz, Russell G
Subject: VIOXX package

Lana,

Here is the final draft for the team leader memo for VIOXX, and the revised professional insert and patient information. Base document is current approved label. Our revised label is currently under review in HFD-550. I am waiting for their input before starting labeling negotiations. Beside labeling, I think we have now a complete package.

Eric

Eric Bastings, M.D.
Acting medical team leader (Neurology)
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

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MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Date:	March 12, 2004
From:	Eric Bastings, MD.
To:	Russell Katz, MD
Subject:	21-647 VIOXX

NDA 21-647 (type 6) received on May 27, 2003 contains information to support the marketing of VIOXX, (VIOXX 25 and 50 mg tablets ————————) for the acute treatment of migraine with and without an aura in adults.

VIOXX (rofecoxib) is a COX-2 non-steroidal anti-inflammatory drug (NSAID) already approved in the United States under NDA 21-042 and 21-052 for the following indications:

- For relief of the signs and symptoms of osteoarthritis (12.5 to 25 mg daily).
- For relief of the signs and symptoms of rheumatoid arthritis in adults (25 mg daily).
- For the management of acute pain in adults (50 mg daily, up to 5 days).
- For the treatment of primary dysmenorrhea (50 mg daily, up to 5 days).

For this application, Dr. Martha Heiman provides the chemistry review. Dr Andrea Powell provides the pharm/tox review. Dr. Wen-Hwein Chou provides the OCPB review. Dr. Khin provides the DSI review. Dr. Kevin Prohaska provides the clinical review. Dr. Sharon Yan provides the biostatistics review. Jeanine Best provides a review of the patient information section of labeling.

In this memo, I describe each component of the application below, along with the relevant conclusions from the respective reviewer. I also describe my recommended labeling changes, taking into account the sponsor's proposed labeling, and the labeling recommendations from the individual reviewers.

Chemistry:

Dr. Heimann notes that the drug products investigated in this NDA are currently approved under NDA 21- 042 and NDA 21- 052, and that the current application proposes use of the same products for a new indication. No CMC changes have been made to the approved drug substance or drug products. This application does not increase the maximum allowed daily intake of the active moiety. In view of the approved status of the products investigated in this NDA, Dr. Heimann recommends approval of the current application.

Pharmacology and Toxicology:

Dr. Powell notes the proposed dosing regimen for VIOXX in the acute treatment of migraine (25 mg or 50 mg, once daily) is consistent with currently approved dosing regimens for other indications (25 mg is the maximum recommended daily dose for chronic treatment of osteoarthritis and rheumatoid arthritis, and 50 mg is the maximum recommended daily dose for acute treatment [< 5 days] of pain and primary dysmenorrhea). Thus, no new toxicology information was required to support the labeling supplement and none was submitted.

Dr. Powell notes that the sponsor has not conducted any studies to delineate the mechanism of action of VIOXX in the treatment of acute migraine. Therefore, Dr. Powell recommends adding the following sentence to the Clinical Pharmacology Section regarding the mechanism of action of VIOXX: "Studies to elucidate the mechanism of action of VIOXX in the acute treatment of migraine have not been conducted." I concur with that recommendation.

Clinical Pharmacology and Biopharmaceutics

Since no new PK information is submitted, Biopharmaceutics did not review this NDA submission, and has no objection to approval.

Dr. Chou notes that the migraine development program is focused on Phase III studies using VIOXX at doses and dosage schedules that are within the limits of the existing approved label. Therefore, no additional PK/ BA studies were required, nor conducted in this program.

Dr Chou notes that, at pre-NDA meeting, the division recommended that the sponsor evaluates whether pharmacokinetics differ in patients during and between migraines. This information was not submitted. Dr. Chou states that the pharmacokinetics of VIOXX in patients during migraine would be useful to know, but that this is not a requirement for filing.

The division also asked that the sponsor discuss the potential pharmacokinetic and pharmacodynamic interactions with concomitant drugs likely to be used in this indication. This was not provided. However, Dr. Chou notes that the VIOXX label contains adequate information on potential metabolism based drug-drug interactions.

Dr Chou states that since this drug may be used in adolescents as well, a pediatric deferral may be more appropriate than a waiver. She recommends a PK study in pediatric and adult patients with a history of migraine.

Division of Scientific Investigations audits

DSI inspected two US sites, Drs. Block and Geisberg, for their conduct in Trial 161. Both investigators conducted the study with [redacted], which is a privately owned company with approximately [redacted] wholly owned clinical research sites nationwide. There were some record keeping deficiencies noted. For the study sites that were inspected, Dr. Khin notes that there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, that all enrolled subjects received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. No underreporting of adverse events was noted. Dr. Khin concludes that data from these centers appear acceptable for use in support of this NDA.

Clinical

Table 1 summarizes the clinical development program for VIOXX in the treatment of migraine.

Table 1: Clinical Development Program for VIOXX in Migraine (from page 6 of Dr. Prohaska review)

Trial #	Vioxx Dose (mg)	Type of Trial	N	Duration	Comments
Trial 161	25, 50	Single Attack Efficacy	557	Single attack	Conducted in the U.S. only.
Trial 162 (acute)	25, 50	Single Attack Efficacy	783	Single attack	Conducted in 16 countries and included an ibuprofen 400 mg arm.
Trial 162 (extension)	25, 50	Multiple Attack Efficacy	635	3 months (8 attacks/month)	Conducted in 16 countries and included an ibuprofen arm but no placebo arm.
Trial 125	25	Migraine Prophylaxis	264	3 months continuous treatment	Included a placebo and montelukast arm.

I will first discuss the efficacy findings in these trials, and then discuss safety and dosing issues.

Efficacy

Trial 161 and the acute segment of Trial 162 are key to the assessment of VIOXX efficacy in the acute treatment of migraine. The primary endpoint for Trial 161 and the acute phase of Trial 162 was Headache Relief at 2 hours. Headache relief had the usual definition of pain reduction from moderate or severe at baseline going to none or mild at 2 hours. As usual for migraine studies, rescue medication was prohibited for the first 2 hours after treatment. The typical secondary endpoints were evaluated, including the key symptoms of nausea, photophobia, and phonophobia, for which efficacy must be demonstrated to get a migraine claim.

Both Trial 161 and 162 enrolled healthy adult individuals with a history of migraine with and without an aura as defined by the IHS. Subjects completing the acute phase of trial 162 were eligible to enter a 3 month extension phase if they continued to meet the original entry criteria.

Dr. Prohaska notes that dose selection for migraine trials was based on the VIOXX analgesia program. The initial recommendation for VIOXX in acute pain is 50 mg with subsequent down-titration as required. The maximum duration of recommended therapy for acute pain and dysmenorrhea is 5 days. The VIOXX analgesia program previously established 7.5 mg as the no-effect dose, 12.5 mg as the minimal effective dose, 25 mg as an effective dose, and 50 mg as the most effective dose.

The Data Analysis Plans were prospectively developed and found acceptable by our biostatisticians. Missing data was handled using a LOCF algorithm. All tests were analyzed using a two-sided test with an alpha of 0.05. Treatment groups were compared through a pairwise contrast in the context of regression models using a step down approach starting with VIOXX 50 mg then VIOXX 25 mg.

Table 2 summarizes the efficacy results (copied from Table 4 of Dr. Prohaska review).

Table 2: Summary of efficacy results

		VIOXX 25 mg	**VIOXX 50 mg**	**Ibuprofen**	**Placebo**
Primary Endpoint					
Percentage of subjects reporting Headache Relief at 2 hours	Trial 161	54.0%	56.7%	NA	33.7%
	p-value*	**=0.001**	**=0.001**		
	Trial 162	59.4%	62.2%	57.7%	29.9%
	p-value*	**=0.001**	**=0.001**	=0.001	
Associated symptoms					
Percentage of subjects reporting nausea at 2 hours	Trial 161	33.0%	30.3%	NA	41.7%
	p-value*	0.111	**0.030**		
	Trial 162	31.2%	29.8%	27.8%	42.2%
	p-value*	**0.023**	**0.013**	**0.001**	
Percentage of subjects reporting photophobia at 2 hours	Trial 161	61.4%	57.5%	NA	71.4%
	p-value*	**0.032**	**0.005**		
	Trial 162	51.1%	49.5%	50.0%	65.2%
	p-value*	**0.004**	**0.002**	**0.003**	
Percentage of subjects reporting phonophobia at 2 hours	Trial 161	52.3%	45.2	NA	64.0%
	p-value*	**0.036**	**=0.001**		
	Trial 162	43.5%	42.6%	38.8%	59.4%
	p-value*	**0.002**	**0.001**	**=0.001**	
Noteworthy Secondary Endpoint					
Percentages of subjects reporting Pain Freedom at 2 hours	Trial 161	19.9%	23.0%	NA	8.0%
	p-value*	**0.002**	**=0.001**		
	Trial 162	26.2%	26.6%	23.8%	5.3%
	p-value*	**=0.001**	**=0.001**	**=0.001**	

Table 2 shows that VIOXX 50 mg was nominally superior to placebo for all key endpoints in both pivotal trials, and that the same was true for VIOXX 25 mg, with the

exception of nausea in Trial 161. The effect size (over 20% for headache relief) was also clinically significant.

No useful efficacy information can be used from the extension phase of Trial 162, for a number of reasons summarized by Dr. Prohaska on page 53 of his review, mostly because there was no prestated hypothesis for this phase of the study and all analyses are considered exploratory.

Trial P125 was a migraine prophylaxis study, and therefore provides no useful information on the efficacy of VIOXX in the acute treatment of migraine.

Overall, I concur that both doses are effective in the acute treatment of migraine. Although there was a slight numerical superiority of the 50 mg dose over the 25 mg dose for most outcome measures, there is no conclusive evidence to support that VIOXX 50 mg is superior to VIOXX 25mg in the acute treatment of migraine.

Safety

This NDA provides safety information after single exposure to VIOXX 25 mg or 50 mg (Trial 161 and acute phase of Trial 162) or multiple exposures to VIOXX 25 mg or 50 mg over a 3 month period (VIOXX 25 mg and 50 mg in the extension phase of Trial 162; VIOXX 25 mg only in prophylaxis Trial 125). Dr. Prohaska notes on page 60 of his review that, in total, 1340 unique individuals received single doses of study medication in Trial 161 and 162, with 377 subjects receiving VIOXX 25 mg, and 388 subjects receiving VIOXX 50 mg. Regarding exposure to multiple doses in Trial 162 (up to 8 attacks treated per month), 268 patients were exposed to VIOXX 25 mg, and 244 were exposed to VIOXX 50 mg. In addition, 89 patients were exposed to daily doses of VIOXX 25 mg for 3 months in Trial 125.

Overall, the safety data from Trial 161 and 162 do not raise any particular safety concern. There was no death or serious adverse event attributed to VIOXX. There were few (1.9-2.5%) adverse dropouts in the extension phase of Trial 162, and no particular safety signal emerged. Table 3 summarizes the most common adverse events seen during Trial 161 and the acute phase of Trial 162. Dr. Prohaska observes that VIOXX 25 mg compares favorably with placebo with only dyspepsia and somnolence appreciably more frequent in VIOXX- than in placebo-treated patients. For VIOXX 50 mg there were more patients complaining about some of the common adverse events listed in Table 3 compared to placebo, but I note that somnolence and dyspepsia were actually less frequent with VIOXX 50 mg than with VIOXX 25 mg, so that it is difficult to draw definite conclusions regarding somnolence and dyspepsia from these data. Dr. Prohaska also notes that there were no statistical differences between groups for each of these adverse events. Overall these adverse event incidences are similar to those of the combined dysmenorrhea and dental studies (23.4% in VIOXX 25 mg and 30.6% in VIOXX 50 mg).

***Table 3:** AE Incidence (=2%) in Trial 161 and 162 (acute phase only, from Table 39 of Dr. Prohaska review)*

	Placebo (N=376)		Rofecoxib 25 mg (N=377)		Rofecoxib 50 mg (N=388)		Ibuprofen 400 mg (N=199)	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients with one or more adverse experiences	97	(25.8)	111	(29.4)	150	(38.7)	56	(28.1)
Abdominal pain upper[¶]	4	(1.1)	4	(1.1)	7	(1.8)	2	(1.0)
Asthenia	2	(0.5)	5	(1.3)	9	(2.3)	8	(4.0)
Dizziness	16	(4.3)	19	(5.0)	26	(6.7)	10	(5.0)
Dry mouth	22	(5.9)	20	(5.3)	24	(6.2)	12	(6.0)
Dyspepsia	3	(0.8)	10	(2.7)	9	(2.3)	4	(2.0)
Gastroenteritis viral NOS[¶]	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	11	(2.9)	9	(2.4)	19	(4.9)	4	(2.0)
Paraesthesia	3	(0.8)	5	(1.3)	9	(2.3)	2	(1.0)
Pharyngitis[¶]	0	(0.0)	0	(0.0)	2	(0.5)	0	(0.0)
Somnolence	7	(1.9)	16	(4.2)	12	(3.1)	7	(3.5)
Vomiting NOS[¶]	8	(2.1)	3	(0.8)	3	(0.8)	2	(1.0)

[¶] Incidences of adverse experiences in the rofecoxib treatment groups were ≥2% in the Extension Phase Population and are shown for comparison purposes of the incidences of specific adverse experiences between the Acute and Extension Phase populations.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
NOS = Not otherwise specified.

An unexpected finding during the 3-month extension phase of Trial 162, is that fewer subjects taking VIOXX 50 mg reported an adverse event then subjects taking VIOXX 25 mg (31.6% compared to 39.2%). The 3-month extension phase of Trial 162 does not show any new findings, as compared to the experience obtained during previous long term studies outlined in the professional label. In addition, the increased incidences of lower extremity edema and hypertension seen in previous long term studies were not observed in the 3-month extension phase of Trial 162.

The safety experience seen during Trial 125 is useful to understand the long term safety (3 months) of VIOXX 25 mg, however it does not address the safety of VIOXX 50 mg over an extended period. I noted in that trial a higher incidence of drug related cardiovascular system adverse events with VIOXX 25 mg (3.4%; hypertension 2.2% and tachycardia 1.1%) than with montekulast (0%) or placebo (0%).

When the acute phase and extension phase populations are considered together, there is no consistent pattern for any specific adverse experience not already described in VIOXX labeling. The migraine-associated adverse events and their incidences were similar to or less than those of the combined osteoarthritis 6-week to 6-month studies of VIOXX 12.5 and 25 mg. Of note, the osteoarthritis database includes a signal for some adverse events which would not be acceptable in the migraine population, namely lower extremity edema and hypertension. These were not seen with the chronic intermittent use of VIOXX in the migraine population.

Regarding long-term safety (up to one year), the division accepted during the development program that the sponsor may attempt to use data collected in rheumatoid

arthritis (RA) and osteoarthritis (OA) populations, and provide a justification for the applicability of these data in the migraine population. The sponsor chose that route. Overall the long term safety data provided by the sponsor includes 3890 subjects taking VIOXX 50 mg daily for at least 6 months and 284 subjects taking VIOXX 50 mg daily for at least 1 year. A large proportion of these data comes from the VIGOR trial, which evaluated the long term safety (up to 1 year) of VIOXX 50 mg in subjects with rheumatoid arthritis. In the VIGOR study approximately 3181 subjects took VIOXX 50 mg daily for 6 months and 57 subjects took VIOXX 50 mg daily for 11 months. I concur that the amount of long term exposure is acceptable.

Dr. Prohaska summarizes the VIGOR study in page 80 of his review. This study was designed to evaluate the comparative GI safety of VIOXX 50 mg once daily (twice the highest dose recommended for chronic use in OA and RA) versus naproxen 500 mg twice daily (common therapeutic dose). VIGOR was a randomized, double-blind study in 8076 patients with rheumatoid arthritis (RA) requiring chronic NSAID therapy. The median duration of therapy was 9 months and the mean age was 58 years. The study showed an unexpected increase in the relative risk for a cardiovascular events in patients randomized to VIOXX 50 mg (RR=2.37; 95% CI 1.39, 4.06; p=0.0016).

Dr. Prohaska notes that long term daily dosing of VIOXX 12.5 or 25 mg has been generally well tolerated when used in OA and RA. Table 4 summarizes the adverse events reported in chronic OA clinical studies. I noted the over three-fold increased incidence of lower extremity edema, and over two-fold increased incidence of hypertension in patients treated with VIOXX 25mg as compared to placebo. Dr. Prohaska notes that this adverse experience profile is similar in patients treated with VIOXX for 1 year or longer. In addition, small increases in serum creatinine, systolic blood pressure, fluid retention, and edema have been noted in some patients. Even though this population is typically older and sicker than the migraine populations, this has implications in the number of monthly doses of VIOXX which can be safely administered in the migraine population.

***Table 4:** Incidence of AEs (=2%) seen in Long-term OA Studies (up to 6 months, doses up to 25 mg) (from Table 51 of Dr. Prohaska review, page 51)*

	Placebo	Rofecoxib 12.5 or 25 mg Daily	Ibuprofen 2400 mg Daily	Diclofenac 150 mg Daily
	(N=783)	(N=2829)	(N=847)	(N=498)
Abdominal pain	4.1	3.4	4.6	5.8
Asthenia/fatigue	1.0	2.2	2.0	2.6
Back pain	1.9	2.5	1.4	2.8
Bronchitis	0.8	2.0	1.4	3.2
Diarrhea	6.8	6.5	7.1	10.6
Dizziness	2.2	3.0	2.7	3.4
Dyspepsia	2.7	3.5	4.7	4.0
Epigastric discomfort	2.8	3.8	9.2	5.4
Headache	7.5	4.7	6.1	8.0
Heartburn	3.6	4.2	5.2	4.6
Hypertension	1.3	3.5	3.0	1.6
Influenza-like disease	3.1	2.9	1.5	3.2
Lower extremity edema	1.1	3.7	3.8	3.4
Nausea	2.9	5.2	7.1	7.4
Sinusitis	2.0	2.7	1.8	2.4
Upper respiratory infection	7.8	8.5	5.8	8.2
Urinary tract infection	2.7	2.8	2.5	3.6

Dr. Prohaska notes that the adverse event profile of long term daily dosing of VIOXX 50 mg in OA and RA has been similar to that found with VIOXX 25 mg daily, except that gastrointestinal symptoms (abdominal pain, epigastric pain, heartburn, nausea, and vomiting), lower extremity edema, and hypertension occurred with increased frequency. Since the use of VIOXX 50 mg is not associated with greater efficacy compared with VIOXX 25 mg in OA or RA, and the incidences of various adverse experiences are higher for VIOXX 50 mg daily than 25 mg daily, current labeling does not recommend chronic use of VIOXX 50 mg.

Dr Prohaska also discusses the applicability of the long term safety seen in OA and RA to migraine. He generally agrees that if these data were used to support the approval of VIOXX 50 mg in the acute treatment of pain (for 5 days), they should be adequate to support the intermittent use of VIOXX (25 and 50 mg) in the acute treatment of pain. Dr. Prohaska notes several issues to consider. The first is whether the populations are similar enough to permit extrapolation of safety data. The second issue is the language the sponsor proposes in labeling for their dosing regimen.

Dr. Prohaska notes that migraineurs tend to be adult females, less than 45 years of age, with few to no other medical conditions. Dr. Prohaska observes that this demographic profile is similar to the patients with primary dysmenorrhea and not too unlike patients in the acute pain studies (dental pain) which also tended to be younger adults (male and female) with few to no medical conditions. The more difficult question is whether the long term safety data from studies involving patients with osteoarthritis and rheumatoid arthritis are applicable to patients with migraine. Although the two populations are not

similar in many ways, Dr. Prohaska would expect the OA and RA populations to be more prone to adverse events since they tend to be older patients, often with multiple medical problems, on multiple co-medications, and use VIOXX daily as opposed to young otherwise healthy migraineurs who will use the product intermittently. For these reasons Dr. Prohaska agrees the long term safety data is relevant and should be considered in the approval of VIOXX for migraine. I generally concur with Dr. Prohaska assessment, with the additional comment that some of the adverse events seen in the OA and RA populations (hypertension, lower extremities edema) would not be acceptable in the migraine population, and were not seen with chronic/intermittent use of VIOXX .

Dr. Prohaska notes that the present label for VIOXX in acute pain has a clear finite statement relative to the duration of treatment (no longer than 5 days of continuous treatment) whereas the duration of treatment for the indication of migraine in the proposed label is confusing, and leaves open the possibility that migraine patients may dose daily with VIOXX 25 mg to treat acute migraine. I certainly concur with Dr. Prohaska that it is not the same for the RA/OA long term safety to support 5 days of VIOXX 50 mg in acute pain and unlimited daily use of VIOXX 25 and 50 mg in acute migraine. I strongly agree that a limit on the number of days per month an individual can treat with the maximum dose of VIOXX must be imposed. As Dr. Prohaska notes, this is especially true since long term uninterrupted daily use of VIOXX 50 mg has been on rare occasions associated with serious adverse events including myocardial infarction and death. I also note the renal side effects seen with chronic use of VIOXX 25 mg. I am also aware of the preliminary results of recent studies of VIOXX in MCI (Mild Cognitive Impairment) and Alzheimer's disease. [redacted] While these data do not have a direct impact on approval of the present NDA, they must be taken into consideration in selecting a safe dosing regimen and maximum number of monthly doses of VIOXX in the chronic intermittent acute treatment of migraine.

All of the above considerations clearly justify, in my opinion, to limit the number of days of treatment allowable to migraine patients not only for VIOXX 50 mg (which is already the case for all indications), but also for VIOXX 25mg. I base this justification on several facts:

- migraine is a intermittently disabling but otherwise benign condition for which several approved therapies are already available
- only therapies with a minimal side effect profile should be used in the migraine population given the availability of alternative therapies
- chronic use of VIOXX 25mg is associated with renal toxicity and possibly with [redacted]
- efficacy has been demonstrated only in the acute treatment of migraine (chronic intermittent use), and not in the prophylactic treatment of migraine (chronic use).

Given that the maximum number of migraine attacks treated in the 3-month extension of Trial 162 was 8 per month, Dr. Prohaska recommends the regimen be limited to 8 doses in any given month. I note that only 44 patients treated 6 attacks per month or more in Trial 162, and that most of the experience relates to patients treating 5 attacks per month or less. Trial 162 provides limited information on the long term safety of VIOXX in the migraine patients, and limited information on which to base the maximum number of treatment days per month. The cutoff between chronic intermittent use and chronic use remains to some degree arbitrary. I believe that a number of 5 doses per month represents a reasonable compromise, sufficiently low to provide reassurance concerning safety issues associated with long-term daily use of VIOXX, and sufficiently high to cover the needs of the vast majority of migraine patients.

Biostatistics

Dr. Sharon Yan concurs that Trial 161 and 162 have demonstrated a statistically significant benefit of VIOXX 50 mg and 25 mg over placebo in the acute treatment of migraine attack with regard to the primary efficacy parameter and a number of secondary efficacy parameters. Dr. Yan concludes that VIOXX is effective as follows:

1. Rofecoxob 50 mg and 25 mg are superior to placebo in providing headache relief at 2 hour post dosing.
2. VIOXX 50 mg is superior to placebo in reducing the migraine- associated symptoms of nausea, photophobia, and phonophobia at 2 hour post dosing.
3. VIOXX 25 mg is superior to placebo in reducing the migraine- associated symptoms of photophobia and phonophobia at 2 hour post dosing. The effect of VIOXX 25 mg with regard to symptom of nausea could not be concluded.
4. There were no statistically significant difference in the effectiveness between VIOXX 50 mg and 25 mg. However, the totality of the data suggested larger benefit of VIOXX 50 mg than VIOXX 25 mg.

Overall, Dr. Yan review supports approval of both doses for the acute treatment of migraine.

Labeling

I will review here below all sections were labeling changes are proposed either by the sponsor or a reviewer.

A. Professional package insert

Note that there are no deletions proposed in the professional insert, only additions.

Clinical Pharmacology

Dr. Powell recommends adding a statement that "Studies to elucidate the mechanism of action of VIOXX in the acute treatment of migraine have not been conducted." I concur with that addition.

Clinical studies

The sponsor added a section on migraine with or without aura.

I reformatted the section in line with the format of recently approved products for the acute treatment of migraine. [redacted]

Indications and usage
I added the standard statement that "The safety and effectiveness of VIOXX have not been established for cluster headache, which is present in an older, predominately male, population."

Adverse reactions
The sponsor added a paragraph on the experience in migraine trials. Dr. Prohaska and I rephrased the section, in line with the data submitted.

Dosage and Administration
The sponsor is not proposing to limit the use of VIOXX 25 mg in the migraine population. The sponsor is only proposing a statement recognizing that chronic use of VIOXX 50 mg is not recommended. For the reasons described above, I concur with Dr. Prohaska that chronic use of VIOXX 25 mg is not recommended in the migraine population. I also believe that a clear limit in the maximum recommended number of doses in any given month must be stated in labeling. In that sense, I added a statement that "The maximum recommended daily dose is 50 mg, not to exceed 5 doses in any given month."

B. Patient product information
This section was reviewed by Jeanine Best and Kevin Prohaska. Jeanine Best is proposing extensive reorganization of the section (with several deletions). I reviewed the final version edited by Dr. Prohaska and concur with the changes.

Recommendation

I recommend approval of VIOXX 25 mg and VIOXX 50 mg for the acute treatment of migraine. I recommend that the total number of doses should not exceed 5 per month. I recommend that pediatric studies in the adolescent population 12-17 be deferred to post-approval.

Eric P. Bastings, M.D.
Acting Team leader, Neurology

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cc:
HFD-120

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/s/

Eric Bastings
3/22/04 06:45:04 PM
MEDICAL OFFICER

MEMORANDUM

Date: March 8, 2004

From: Andrea M. Powell, Ph.D.
Division of Neuropharmacological Drug Products (HFD–120)

Subject: NDA 21-647

NDA 21-647 was filed on July 26, 2003 as a labeling supplement for the approval of Vioxx® for the acute treatment of migraine with and without aura (in adults). Based on the current labeling, Vioxx® is approved for the following indications in adults: for the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis, for the management of acute pain, and for the treatment of primary dysmenorrhea.

The proposed dosing regimen for Vioxx® in the acute treatment of migraine (25 mg or 50 mg, once daily) is consistent with currently approved dosing regimens for other indications (25 mg is the maximum recommended daily dose for chronic treatment of osteoarthritis and rheumatoid arthritis, and 50 mg is the maximum recommended daily dose for acute treatment [$\leq$ 5 days] of pain and primary dysmenorrhea). Thus, no new toxicology information was required to support the labeling supplement and none was submitted.

In our letter to the sponsor dated July 31, 2003, we stated that "... it would be helpful to know what information you have regarding the proposed mechanism of action of Vioxx® in the treatment of migraine." We asked the sponsor to "... provide a summary of the available information and copies of the relevant references." The sponsor submitted their response on August 25, 2003. According to the sponsor:

> "The exact anti-migraine mechanism of action for the NSAIDs is unknown. Preclinical and clinical studies on mechanisms involved in migraine pathogenesis indicate that the activation of meningeal trigeminal afferent nerve fibers that occurs during a migraine attack is associated with a release of sensory neuropeptides that can trigger the production and release of inflammatory mediators such as prostaglandins. It has been hypothesized that these inflammatory mediators intensify migraine headache pain by sensitizing trigeminal nociceptive pathways and amplifying pain signal transmission. (see Burstein R: Pain 89;2001: 107-110: Deconstructing migraine headache into peripheral and central sensitization for short review). Reduced production of prostaglandins through the inhibition of COX-2 that is induced by painful inflammation may therefore prevent sensitization of trigeminal pain neurons and provide migraine headache relief."

The sponsor has not conducted any studies to delineate the mechanism of action of Vioxx® in the treatment of acute migraine. Therefore, consideration should be given to adding the following sentence to the Clinical Pharmacology Section regarding the mechanism of action of Vioxx®: "Studies to elucidate the mechanism of action of VIOXX in the acute treatment of migraine have not been conducted." The text of the sponsor's proposed labeling follows and is presented in italics. The suggested modification to the labeling is presented in bold and is underlined.

Mechanism of Action

VIOXX is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of VIOXX is believed to be due to inhibition of prostaglandin synthesis, via inhibition of cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, VIOXX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. **Studies to elucidate the mechanism of action of VIOXX in the acute treatment of migraine have not been conducted**.

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

/s/

Andrea Powell
3/8/04 01:14:57 PM
PHARMACOLOGIST

Lois Freed
3/8/04 01:25:44 PM
PHARMACOLOGIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 24, 2004

TO: Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
HFD-120

VIA: Laura Yan Chen, Regulatory Project Manager
Division of Neuropharmacological Drug Products
HFD-120

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Vioxx (rofecoxib tablets [redacted]), NDA 21-647

Background and Summary

The sponsor submitted a Type 6 NDA on May 23, 2003, for Vioxx (rofecoxib tablets [redacted]), NDA 21-647, to expand the indication to include the acute treatment of migraine attacks with or without aura in adults.

The patient labeling which follows represents the revised risk communication materials of the patient information for Vioxx. It has been reviewed by our office and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. The revisions are also based on the recent recommended revisions for other COX-2 inhibitor products.

These revisions are based on labeling (PI) submitted by the sponsor on May 23, 2003. Patient information should always be consistent with the prescribing information. All future changes to

the PI should also be reflected in the PPI.

Comments
We also have the following comments:

1. We continue to recommend class PPI labeling for the COX-2 inhibitor products for labeling consistency across these products.
   - Keep the current Medication Guide question and answer type format as this format has research and experience to support its communication effectiveness.
   - Ensure that the vocabulary and sentence structure is simplified for low literacy readers. A 6th to 8th grade reading comprehension level and a reading ease score of at least 60% is optimal for all patient materials.
   - Avoid the use of clinical data information in PPIs. This information is difficult for most patients, especially those with low literacy to interpret, and does not add meaning to the risk information.
   - Avoid partial lists of medications in patient information. Either list all generic and tradenames, or list the name of the drug class and add a statement for the patient to check with their doctor or pharmacist if they are not sure if their medications are in a specific class. Patients feel 'safe' if a list of medications fails to include the name of their medication.
   - Remove any promotional language per DDMAC guidelines.

2. The PI states (PRECAUTIONS: *Information for Patients section)* that "Physicians should instruct their patients to read the patient package insert before starting therapy with VIOXX and to reread it each time the prescription is renewed in case any information has changed." What mechanism does the sponsor have in place to ensure that a PPI is dispensed with each prescription? Vioxx is not always dispensed in unit of use packages and there is no requirement for PPIs to be dispensed with prescriptions. In general, pharmacies do not stock bulk PPIs, nor make copies of a single PPI for dispensing purposes. We recommend deleting this statement from the PI unless there is a mechanism in place for getting the PPI to patients with each prescription or refill.

Comments to the review division are bolded, underlined and italicized. We can provide a marked-up and clean copy of the revised document in Word if requested by the review division. Please call us if you have any questions.

Patient Information

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Administrative- 2

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/s/

Jeanine Best
2/24/04 03:13:04 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
2/25/04 10:28:08 AM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

N 21-647

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Harry I. Geisberg, M.D.

Food and Drug Administration
Rockville MD 20857

JAN 29 2004

Dear Dr. Geisberg:

On September 8 and 9, 2003, Ms. Stephanie E. Hubbard, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol 161 entitled "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Groups Study to Examine the Safety, Tolerability, and Efficacy of Rofecoxib 50 and 25 mg for the Acute Treatment of Migraine") of the investigational drug rofecoxib (Vioxx), performed for Merck. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that during the inspection, Ms. Hubbard's discussion with you included the followings:

1. You did not maintain adequate and accurate records [21 CFR 312.62(b)].

   a. You did not maintain the faxed screening laboratory results you reviewed prior to the enrollment of all study subjects, with the exception of one subject.

   b. The protocol inclusion criteria specified that the patient must have, on average, ≥ 1 and ≤ 8 migraines per month for the past six months. You indicated in the checklist used in the study that this criterion was met for all subjects. You did not document the patients' actual attack level (number of migraines) in the source document.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Hubbard during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: [redacted]
Field Classification: NAI pending review by HQ
Headquarters Classification:
_____1)NAI
__X _2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

If Headquarters classification is a different classification, explain why: record keeping discussed during the inspection.

Deficiencies noted:
__X__Inadequate and inaccurate records (06)

cc:
HFA-224
HFD-120 Doc.Rm. NDA 21-647
HFD-120 Review Div.Dir. Katz
HFD-120 MO Prohaska
HFD-120 PM Chen
HFD-46 c/r/s GCP File #11097
HFD-46 MO Khin
HFR-SE150 DIB Todd-Murrell
HFR-SE150 Bimo Monitor & Field Investigator Hubbard
GCF-1 Seth Ray

r/d: NK:1/21/04
reviewed: KMU:1/04
f/t:sg:1/22/04

O:\NK\Letters\Geisberg.vai.doc

Reviewer Note to Rev. Div. M.O.

- For protocol 161, 18 subjects were screened and randomized; 14 subjects completed the study.
- An audit of 9 subjects' records (1181, 1184, 1185, 1189, 1191, 1192, 1195, 1196, and 1198) was conducted.
- No discrepancies were observed between the source data and data listing reported in the NDA.
- No serious adverse events reported at this site.
- No FDA Form-483 was issued. However, the discussion during the inspection included:
  1) All faxed screening laboratory results reviewed by the physician prior to enrollment, with the exception of one, were not retained. The site documented this deficiency in a memo to

file. The study coordinator thought that the monitor may have collected these results and failed to return them to the files.

2) The inclusion criteria specified that the patient has on average ≥ 1 and ≤ 8 migraines per month for the past six months. The checklist used in the study indicates that this criterion has been met for all subjects. The source data did not document the patients' actual attack level (number of migraines).
3) Four subjects were noted to have their visits outside the window specified in the protocol (1186, 1191, 1196 and 1198). Waivers were obtained from the sponsor.

- Overall, data appear acceptable.

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Khin U
1/29/04 02:09:18 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: January 12, 2004

TO: Lana Chen, R.Ph., Senior Regulatory Project Manager
Kevin Prohaska, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Khin Maung U, M.D., Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 21-647

APPLICANT: Merck Research Laboratories

DRUG: Rofecoxib (Vioxx) Tablets

THERAPEUTIC CLASSIFICATION: Standard Review

PROPOSED INDICATION: Treatment of Acute Migraine

CONSULTATION REQUEST DATE: July 2, 2003

ACTION GOAL DATE: March 27, 2004

I. BACKGROUND:

Rofecoxib (Vioxx) is a nonsteroidal anti-inflammatory drug (NSAID), approved for treatment of osteoarthritis, rheumatoid arthritis and analgesia including dysmenorrhea. In this application, the sponsor has requested for the acute treatment of migraine. The application is based on two double-blind, placebo-controlled, multicenter studies (protocols 161 and 162 entitled "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Groups Study to Examine the Safety, Tolerability, and Efficacy of Rofecoxib 50 and 25 mg for the Acute Treatment of Migraine."

The inspection assignment was issued in August 2003 for two US sites: Drs. Block and Geisberg for their conduct in the protocol 161. Both investigators conducted the study with

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Administrative- 3

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/s/

Ni Aye Khin
1/13/04 09:56:04 AM
MEDICAL OFFICER

Khin U
1/14/04 04:47:11 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2006
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Merck & Co., Inc.	May 23, 2003
TELEPHONE NO. *(include Area Code)*	**FACSIMILE (FAX)** *Number (include Area Code)*
484-344-7026	484-344-2516
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Sumneytown Pike, P. O. Box 4, BLA-20 West Point, PA 19486	Peter J. Basseches, Ph.D. Director, Regulatory Affairs

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-647

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Rofecoxib	VIOXX™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*
4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone

CODE NAME *(If any)* N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	25 mg, 50 mg, 25 mg/5 mL	Oral

(PROPOSED) INDICATION(S) FOR USE:
Acute Treatment of Migraine

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUALREPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT *(Rx)* ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Attached document provides the establishment and PAI readiness information for this product.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CIFIR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
X	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
X	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
X	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
X	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601-2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or 0)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.50 (k)(3))
X	18. User Fee Cover Sheet (Form FDA 3397)
X	19. Financial Information (21 CFR Part 54)
X	20. OTHER (Specify) Pediatric Use Information; Regulatory Background Information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contra i nd ications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Peter J. Basseches	Peter J. Basseches, Ph.D. Director, Regulatory Affairs	May 23, 2003

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Sumneytown Pike, P. O. Box 4, BLA-20 West Point, PA 19486	(484) 344-7026

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Attachment to 356h Form
NDA 21-647
Merck & Co. Inc.
VIOXX™ (rofecoxib) tablets

ESTABLISHMENT INFORMATION:

Drug Substance:

Manufacturer
Merck Manufacturing Division

1) Merck Sharp & Dohme (Singapore) Ltd.
21 Tuas South Avenue 6
Singapore 637766

CFN – 3003431146/67317

2) Merck & Co. Inc.
126 E. Lincoln Avenue
Rahway, NJ 07065-0900

CFN - 2211017

Drug Product:

Manufacturer
Merck Manufacturing Division

1) Merck Sharp & Dohme
Quimica de Puerto Rico, Inc.
Road #2, Kilometer 60.3
Sabana Hoyos
Arecibo, PR 00688

CFN - 2650235

2) Merck Sharp & Dohme (Australia) Pty Ltd.
54-68 Ferndell Street
South Granville, NSW 2142 Australia

CFN – 9613614/62904

Attachment to 356h Form (Cont.)
NDA 21-647
Merck & Co. Inc.
VIOXX™ (rofecoxib) tablets

Packager
Merck Manufacturing Division

1) Merck Sharp & Dohme
Quimica de Puerto Rico, Inc.
Road #2, Kilometer 60.3
Sabana Hoyos
Arecibo, PR 00688

CFN - 2650235

2) Merck & Co., Inc.
4633 Merck Road
Wilson, NC 27893

CFN – 1036761

Contract Facility

Peter J. Basseches, Ph.D.
Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486
Tel 484 344 7026
Fax 484 344 2516
Email: peter_basseches@merck.com

May 23, 2003

MERCK
Research Laboratories

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Katz :

NDA 21-647: VIOXX™ (Rofecoxib)

ORIGINAL NEW DRUG APPLICATION

User Fee ID # 4533

Pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act, and in accordance with Title 21 of the Code of Federal Regulations, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is submitting for the Agency's review and approval, a Type 6 New Drug Application (NDA) for VIOXX™ (also referred to as rofecoxib, MK-0966, and L-748731). This NDA submission provides clinical support for the use of rofecoxib 25 and 50 mg in the acute treatment of migraine, with or without aura, in adults.

Reference is made to the April 3, 2001 End-of-Phase II Meeting between representatives of FDA and MRL regarding the rofecoxib development program for acute migraine treatment and to the Pre-NDA Meeting for this application held on December 4, 2002. Reference is also made to a April 15, 2003 phone conversation between Dr. Peter Basseches (MRL, Director, Regulatory Affairs) and Ms. Lana Chen (FDA, Project Manager, Division of Neuropharmacological Drug Product) during which the Agency confirmed that, although this NDA is a new application to the Division of Neuropharmacological Drug Products, for administrative and review purposes, this application will be treated as a supplemental application to the NDAs #21-042 (rofecoxib tablets) and #21-052 (rofecoxib oral suspension) for VIOXX™ previously approved by the Division of Antiinflammatory, Analgesics and Ophthalmologic Drug Products. Therefore, reference is made to the approved NDAs for VIOXX™ 21-042 (rofecoxib tablets) and 21-052 (rofecoxib oral suspension) and to the supplements submitted to those NDAs post-approval; a list of these supplements is provided as an attachment to this cover letter.

Migraine is a common neurological disorder usually characterized by attacks of moderate or severe headache, associated with nausea, vomiting, photophobia and phonophobia, and, in approximately 10-20% of patients, preceded by aura. Based on their efficacy and relatively good tolerability, nonsteroidal antiinflammatory drugs (NSAIDs) are often utilized as first-line treatment. Indeed, approximately 40% (U.S.) to 50% (non-U.S.) of drugs prescribed for migraine are NSAIDs. Traditional NSAIDs, which are nonselective inhibitors of COX-1 and COX-2, have been shown in clinical trials to be effective for the acute treatment of migraine headache. Rofecoxib is a selective cyclooxygenase (COX)-2 inhibitor that was initially approved by the FDA in 1999. It is currently indicated for the chronic treatment of osteoarthritis (12.5 to 25 mg daily) and rheumatoid arthritis (25 mg daily), as well as for the treatment of acute pain and primary dysmenorrhea (50 mg daily up to 5 days). Rofecoxib has been shown to be effective in three clinical models of acute pain: postoperative dental pain, post-orthopedic surgical pain, and primary dysmenorrhea.

This NDA submission provides clinical support for the use of rofecoxib 25 and 50 mg in the acute treatment of migraine, with or without aura, in adults. Since the rofecoxib development program for acute migraine treatment involved a marketed product, development efforts have focused on a Phase III clinical development program. Therefore, this application contains information from two pivotal, multicenter, placebo-controlled, double-blind, randomized trials (Protocols 161 and 162) that were similar in design, as well as an additional trial considered supportive of long-term safety that evaluated the use of rofecoxib in the prevention of migraine (Protocol 125). Protocol 161 was conducted entirely within the U.S., while Protocol 162 was multinational (U.S. plus non-U.S.) and included an active comparator treatment arm and a 3-month extension phase. The acute phase of each of the pivotal studies utilized rofecoxib doses of 25 and 50 mg and involved treatment of a single migraine attack. The extension phase of Protocol 162 included many features of a separate controlled trial; it was placebo-controlled, double blinded, had its own data analysis plan (DAP), and was reported in a separate clinical study report (CSR). Furthermore, while the extension phase utilized the same patients as the acute phase, treatment assignments were re-randomized for the extension.

These studies showed that, in the acute treatment of migraine, significantly more patients treated with rofecoxib reported relief of headache and associated symptoms of photophobia, phonophobia, and nausea at 2 hours, compared to patients treated with placebo. Patients treated with rofecoxib also showed clinically significant improvements in other signs and symptoms of migraine, compared to placebo, including pain freedom within 2 hours, 24-hour sustained headache relief and pain freedom, reduction in the need for additional medication between 2-24 hour, and improvement in functional disability within 2 hours. Rofecoxib 25 mg and 50 mg continued to be effective when used intermittently for the acute treatment of migraine attacks over longer time periods (12 weeks). Rofecoxib was effective regardless of race, age, gender, presence of aura, presence of menses or dysmenorrhea. Additionally, rofecoxib efficacy was not affected by concomitant use of common prophylactic migraine drugs, oral contraceptives, or

previous response to NSAIDs. Rofecoxib 25 mg provides significant efficacy in the acute treatment of migraine, and is proposed as the recommended starting dose in most patients. However, some patients may derive additional benefit with 50 mg as evidenced by consistent numerical efficacy advantages over 25 mg on multiple endpoints, and significant superiority for 24-hour sustained headache relief.

These studies also demonstrated that rofecoxib 25 mg and 50 mg are well tolerated when used for the acute treatment of intermittent migraine attacks.

This NDA is formatted according to the International Conference on Harmonization (ICH) Common Technical Document (CTD) guidelines and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, MRL is providing two Compact Disks (CD), which contain the submission. All documents requiring signatures for certification are included as paper for archival purposes. The Microsoft WORD version of the proposed labeling text (proposed.doc) is contained within the labeling folder on the electronic medium provided. Review copies are also being submitted in hard copy as described in the Statement of Organization following the cover letter. As agreed upon during the December 4, 2002 Pre-NDA Meeting cited above, Chemistry, Manufacturing, Controls (with the exception of a request for categorical exclusion for Environmental Assessment), Nonclinical Pharmacology and Toxicology, and Human Pharmacokinetic and Bioavailability documentation are not contained within this application because no new information relating to these sections have been generated for the purpose of this NDA. We refer the Agency to the approved NDA 21-042 for VIOXX™ for a review of this information. The Statement of Organization following this letter describes the sections contained in this application.

We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.51, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Neuropharmacological Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Lana Chen, Regulatory Health Project Manager.

Reference is made to 21 CFR Part 54, *Financial Disclosure of Investigators.* Data from multiple clinical studies are included in this application. Financial Disclosure certification and disclosure information as outlined in the regulations are provided under Item 19.

In accordance with the Prescription Drug User Fee Act of 1992 (PDUFA), and reauthorized in the Food and Drug Administration Modernization Act of 1997 (FDAMA), a check (Check No. C08139132) in the amount of $266,700 was sent to the Mellon Client Services Center (FDA 360909), Rm. 670, 500 Ross Street, Pittsburgh, PA 15262-0001, on April 30, 2003. The User Fee I.D. number is 4533.

Merck is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(b). The patient use of rofecoxib meets the requirements of a categorical exclusion under 21 CFR §25.31(b) because the estimated concentration of the active drug substance at the point of entry, referred to as the Expected Introduction Concentration (EIC), into the aquatic environment will be below 1 part per billion (ppb). To Merck's best knowledge, no extraordinary circumstances exist in regards to this action.

We consider the filing of this NDA 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.

Questions concerning this submission should be directed to Peter J. Basseches, Ph.D. (484-344-7026) or, in my absence, to Michelle W. Kloss, Ph.D. (484-344-2905).

Sincerely,

Peter J. Basseches

Peter J. Basseches, Ph.D.,
Director, Regulatory Affairs

Enclosure: CDs (2)

Hand Deliver

Q:\Lesher\Migraine\NDA Docs\NDA Cover Letter FINAL.doc

Desk Copies: Ms. Lana Chen, Regulatory Project Manager (cover letter, administrative volume)
HFD-120, Room 4031

Maryann Holovac (cover letter and patent)
Orange Book Staff
Office of Generic Drugs
HFD-610, Room 134
7500 Standish Place
Rockville, MD 20855-2773

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-647	Efficacy Supplement Type	Supplement Number	
Drug: Vioxx (rofexocib) Tablets [redacted]		Applicant: Merck	
RPM: Lana Chen, R.Ph.		HFD-120	Phone # 301-594-5529
Application Type: (x) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NDA 21-042 rofecoxib tablets NDA 21-052 rofecoxib suspension	

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	6
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	10 month= 3/26/04
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
User Fee Information	
• User Fee	(x) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(x) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(x) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

Exclusivity Summary (approvals only)	See Tab D
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	(✓) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(✓) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(✓) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(✓) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	See Tab C
• Most recent applicant-proposed labeling	See Tab C
• Original applicant-proposed labeling	See Tab C
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	See Tab C for ODS, DDMAC reviews
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	See Tab C
• Applicant proposed	See Tab C
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	No
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	See Tab G
❖ Clinical review(s) *(indicate date for each review)*	See Tab H
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See Clinical Review Tab H
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	See Tab E
❖ Statistical review(s) *(indicate date for each review)*	See Tab J
❖ Biopharmaceutical review(s) *(indicate date for each review)*	See Tab K
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	See Tab I
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	See Tab N ✓
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**(X)** Completed **( )** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	See Tab R
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

STATEMENT OF ORGANIZATION

NDA 21-647: VIOXX™ (Rofecoxib)

Original New Drug Application

This submission contains the following paper and/or electronic information:

ITEM(s)	DESCRIPTION	Contents on Archival CD	Archival Copy	Paper Review Copies
1,13,16,17, 18,19,20	Administrative Data	Yes	Blue Binder (1 Volume)	Red Binder, Green Binder, Tan Binder (1 volume each)
2	Labeling*	Yes	No	
3	Synopsis of Application	Yes	No	
4	Chemical and Pharmaceutical Manufacturing and Controls Documentation	Yes	No	Red Binder (1 Volume)
8,10	Clinical and Statistical Documentation	Yes SAS Dataset as .xpt and SAS programs as .sas are located in the CRT folder.	No	Green Binder (1 Volume) Tan Binder (1 Volume)
11	Case Report Tabulations	Yes (SAS transport files)	No	No
12	Case Report Forms	Yes	No	No

TOTAL VOLUMES: 7

(NOTE: The total number of volumes above equals the total number of volumes received by FDA - archival plus paper review copies. The total number of volumes entered on the 356H is the total number of volumes contained in the archival copy)

*The WORD version of the proposed labeling text is provided on archival CD.

Supplements to NDA 21-042 VIOXX™ (rofecoxib tablets)

Supplement No.	Date of Submission	Date of Approval (A)/ Date of Implementation (I)/ Date of Withdrawal (W)	Nature of Supplement
S-001	7/15/99	2/25/00 (A)	This supplement provides chemistry and labeling changes to support a 50 mg tablet.
S-002	5/26/99	10/28/99 (A)	This supplement provides for a revised proposal for a Patient Package Insert (PPI).
S-003	10/6/99	3/17/00 (A)	This cbe provides for circular revisions to include post-marketing adverse reactions and post-marketing experience of concurrent administration of clinical doses of VIOXX™ with warfarin. In addition, Merck's pregnancy registry information, including an "800" number, was added and the company address was changed. 10/28/99 Acknowledgment letter from the Agency informing us that this supplement should not be a CBE. An approved supplement is required.
S-004	10/6/99	3/7/00 (A)	This supplement provides for revisions to the dissolution specification for VIOXX™ 12.5 and 25 mg tablets from Q= ━ in 20 minutes to Q= ▬ in 20 minutes.
S-006	4/7/00	8/10/00 (A)	This Supplement provides for the addition of the ▬▬▬▬▬▬▬▬ manufacturing facility as an alternate source for Tablets VIOXX™ 12.5 and 25 mg.
S-007	6/29/00	4/11/02 (A)	This supplement provides for revisions to the following sections of the label: CLINICAL PHARMACOLOGY, CLINICAL STUDIES, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS. These labeling revisions are a result of the **VI**OXX™ **G**astrointestinal **O**utcomes **R**esearch study (**VIGOR**).
S-008	7/10/00	4/11/02 (A)	This supplement provides for changes to the US Package Insert and US Patient Product Information. Proposed revisions are made to the following sections of the label: CLINICAL PHARMACOLOGY, and PRECAUTIONS. The label has been revised to include new pharmacokinetic data in patients with moderate hepatic insufficiency, information on a potentially significant drug interaction with theophylline and information on the lack of a significant drug interaction with methotrexate when rofecoxib is administered at the recommended doses.

Supplements to NDA 21-042 VIOXX™ (rofecoxib tablets) - Continued

Supplement No.	Date of Submission	Date of Approval (A)/ Date of Implementation (I)/ Date of Withdrawal (W)	Nature of Supplement
S-009	9/11/00	1/10/01 (A)	This CMC supplement provides for minor modifications to the tablet size of VIOXX™, 25 and 50 mg tablets to address marketing preferences. The tablets will be compressed to slightly smaller diameters and as a result, have higher hardness targets and ranges.
S-010	9/29/00	4/11/02 (A)	This supplement (CBE) provides for changes to the US Package Insert and US Patient Product Information to include post-marketing adverse reactions and post-marketing experience of concurrent administration of clinical doses of VIOXX™ with lithium.
S-011	2/16/01	6/13/01 (A)	This CBE-30 provides for an alternate location for stability testing for VIOXX™ at Merck's Wilson, North Carolina site.
S-012	2/28/01	4/11/02 (A)	This supplement provides for changes to the US Package Insert and US Patient Product Information to include a **Rheumatoid Arthritis** indication. Proposed revisions are made to the following sections of the label: CLINICAL STUDIES, INDICATIONS AND USAGE, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.
S-013	4/5/01	4/11/02 (A)	This supplement (CBE) provides for changes to the US Package Insert and US Patient Product Information to include post-marketing adverse reactions.
S-014	10/2/01	4/11/02 (A)	This supplement (CBE) provides for changes to the US Package Insert and US Patient Product Information to include post-marketing adverse reactions.
S-015	12/7/01	6/6/02 (A)	This CBE-30 provides for the addition of Merck's South Granville, Australia manufacturing facility as an alternate source for Tablets VIOXX™ 50 mg in the US.
S-016	1/14/02	6/25/02 (A)	Prior Approval Supplement supporting the addition of the Merck Manufacturing Division (MMD) Singapore facility as an additional site of manufacture for rofecoxib drug substance.

Supplements to NDA 21-042 VIOXX™ (rofecoxib tablets) - Continued

Supplement No.	Date of Submission	Date of Approval (A)/ Date of Implementation (I)/ Date of Withdrawal (W)	Nature of Supplement
S-017	4/23/02		This supplement (CBE) provides for labeling changes to the package circular to add the updated copyright date of 2002 and to add post-marketing adverse experiences.
S-018	10/14/02		This supplement (PAS) provides for labeling changes to the package circular to include a brief description of the aspirin endoscopy study (136). In addition the dosage for patients with moderate hepatic insufficient has been further clarified. Proposed revisions are made to the following sections of the label: CLINICAL STUDIES and DOSAGE AND ADMINISTRATION
[redacted]			
S-020	12/11/02		This supplement (CBE) provides for changes to the US Patient Product Information to include post-marketing adverse reactions
S-021	5/5/03		This supplement (CBE) provides for changes to the US Patient Product Information to include post-marketing adverse reactions

Supplements to NDA 21-052 VIOXX™(rofecoxib oral suspension)

Supplement No.	Date of Submission	Date of Approval (A)/ Date of Implementation (I)/ Date of Withdrawal (W)	Nature of Supplement
S-001	5/26/99	10/28/99 (A)	This supplement provides for a revised proposal for a Patient Package Insert (PPI).
S-002	9/2/99	3/2/00 (A)	This supplement provides for 24 month real time stability data for VIOXX™ oral suspension packaged in the glass bottles to support a 24-month expiration date.
S-004	6/29/00	4/11/02 (A)	This supplement provides for revisions to the following sections of the label: CLINICAL PHARMACOLOGY, CLINICAL STUDIES, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS. These labeling revisions are a result of the **VI**OXX™ **G**astrointestinal **O**utcomes **R**esearch study (**VIGOR**).
S-003	10/6/99	3/17/00 (A)	This CBE provides for circular revisions to include post-marketing adverse reactions and post-marketing experience of concurrent administration of clinical doses of VIOXX™ with warfarin. In addition, Merck's pregnancy registry information, including an "800" number, was added and the company address was changed. 10/28/00 Acknowledgement letter from the Agency informing us that this supplement should not be a CBE. An approved supplement is required.
S-005	7/10/00	4/11/02 (A)	This supplement provides for changes to the US Package Insert and US Patient Product Information. Proposed revisions are made to the following sections of the label: CLINICAL PHARMACOLOGY, and PRECAUTIONS. The label has been revised to include new pharmacokinetic data in patients with moderate hepatic insufficiency, information on a potentially significant drug interaction with theophylline and information on the lack of a significant drug interaction with methotrexate when rofecoxib is administered at the recommended doses.

Supplements to NDA 21-052 VIOXX™(rofecoxib oral suspension) - Continued

Supplement No.	Date of Submission	Date of Approval (A)/ Date of Implementation (I)/ Date of Withdrawal (W)	Nature of Supplement
S-006	9/29/00	4/11/02 (A)	This supplement (CBE) provides for changes to the US Package Insert and US Patient Product Information to include post-marketing adverse reactions and post-marketing experience of concurrent administration of clinical doses of VIOXX™ with lithium.
S-007	2/28/01	4/11/02 (A)	This supplement provides for changes to the US Package Insert and US Patient Product Information to include a **Rheumatoid Arthritis** indication. Proposed revisions are made to the following sections of the label: CLINICAL STUDIES, INDICATIONS AND USAGE, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.
S-008	4/5/01	4/11/02 (A)	This supplement (CBE) provides for changes to the US Package Insert and US Patient Product Information to include post-marketing adverse reactions.
S-009	10/2/01	4/11/02 (A)	This supplement (CBE) provides for changes to the US Package Insert and US Patient Product Information to include post-marketing adverse reactions.
S-010	1/14/02	6/25/02 (A)	Prior Approval Supplement supporting the addition of the Merck Manufacturing Division (MMD) Singapore facility as an additional site of manufacture for rofecoxib drug substance.
S-011	4/23/02		This supplement (CBE) provides for labeling changes to the package circular to add the updated copyright date of 2002 and to add post-marketing adverse experiences.

Supplements to NDA 21-052 VIOXX™(rofecoxib oral suspension) - Continued

Supplement No.	Date of Submission	Date of Approval (A)/ Date of Implementation (I)/ Date of Withdrawal (W)	Nature of Supplement
S-012	10/14/02		This supplement (PAS) provides for labeling changes to the package circular to include a brief description of the aspirin endoscopy study (136). In addition the dosage for patients with moderate hepatic insufficient has been further clarified. Proposed revisions are made to the following sections of the label: CLINICAL SECTIONS and DOSAGE AND ADMINISTRATION.
S-014	12/11/02		This supplement (CBE) provides for changes to the US Patient Product Information to include post-marketing adverse reactions.
S-015	5/5/03		This supplement (CBE) provides for changes to the US Patient Product Information to include post-marketing adverse reactions.