CENTER FOR DRUG EVALUATION AND RESEARCH

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

ADMINISTRATIVE DOCUMENTS

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-042 NDA 21-052	Efficacy Supplement Type SE-8	Supplement Number: 007 004	
Drug: Vioxx (rofecoxib tablets) Tablets 12.5 mg, 25 mg 50 mg Vioxx (rofecoxib suspension) Suspension 12.5 mg/5 mL, 25 mg/5 mL		Applicant: Merck & Co., Inc.	
RPM: Barbara Gould		HFD-550	Phone #: 301 827-2090
Application Type: (✔) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A	

❖ Application Classifications:	
• Review priority	(✔) Standard ( ) Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	October 10, 2002
❖ Special programs (indicate all that apply)	( ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(✔) 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 (✔) No
• This application is on the AIP	( ) Yes (✔) 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.	(✔) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(✔) 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 (approvals only)	
• Exclusivity summary	✔
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (✔) No
❖ 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)	AE April 06, 2001 AE January 11, 2001
• 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)	
• Most recent applicant-proposed labeling	✔
• Original applicant-proposed labeling	✔
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	N/A
• 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)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• 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)	April 10, 2000
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	

❖ Advisory Committee Meeting	
• Date of Meeting	February 08, 2001
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	N/A
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	April 03, 2001 December 08, 2001
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Included in clinical review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	✔
❖ Statistical review(s) *(indicate date for each review)*	March 23, 2001
❖ Biopharmaceutical review(s) *(indicate date for each review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	March 28, 2001
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	N/A
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	March 23, 2001
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-042 NDA 21-052	Efficacy Supplement Type SE-1	Supplement Number: 012 007	
Drug: Vioxx (rofecoxib tablets) Tablets 12.5 mg, 25 mg 50 mg Vioxx (rofecoxib suspension) Suspension 12.5 mg/5 mL, 25 mg/5 mL		Applicant: Merck & Co., Inc.	
RPM: Barbara Gould		HFD-550	Phone #: 301 827-2090
Application Type: (✓) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A	

❖ Application Classifications:	
• Review priority	(✓) Standard ( ) Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	October 10, 2002
❖ Special programs (indicate all that apply)	( ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(✓) 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 (✓) No
• This application is on the AIP	( ) Yes (✓) 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.	(✓) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(✓) 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 (approvals only)	
• Exclusivity summary	✓
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (✓) No
❖ 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)	AE December 21, 2001
• 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)	
• Most recent applicant-proposed labeling	✓
• Original applicant-proposed labeling	✓
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	
• 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)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• 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)	February 08, 2000
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	

Advisory Committee Meeting	N/A
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	N/A
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	December 20, 2001
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	December 20, 2001
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	✓
❖ Statistical review(s) *(indicate date for each review)*	August 29, 2001
❖ Biopharmaceutical review(s) *(indicate date for each review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
CMC review(s) *(indicate date for each review)*	April 13, 2001
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	March 23, 2001
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-042 / SE1- 012 **and** NDA 21-052/ SE1- 007

Drugs: Vioxx (rofecoxib) Tablets 12.5 and 25 mg Applicant: Merck & Co., Inc.

Vioxx (rofecoxib) Suspension 12.5/5 and 25/5 mL

RPM Barbara Gould Phone 301 827-2090

☒ 505(b)(1)
☐ 505(b)(2) Reference listed drug

☐ Fast Track ☐ Rolling Review Review priority: ☒ S ☐ P

Pivotal IND(s)

Application classifications:
Chem Class 1
Other (e.g., orphan, OTC)

PDUFA Goal Dates:
Primary October 10, 2002
Secondary

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☒ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption
- Action Letter..... ☒ AP ☐ AE ☐ NA
- Labeling & Labels
  FDA revised labeling and reviews.....
  Original proposed labeling (package insert, patient package insert) .....
  Other labeling in class (most recent 3) or class labeling.....
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☐ No
  Immediate container and carton labels .....
  Nomenclature review .....
- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☒ is not on the AIP.
  Exception for review (Center Director's memo).....
  OC Clearance for approval.....

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☐ Materials requested in AP letter

- Post-marketing Commitments — N/A
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....

- Was Press Office notified of action (for approval action only)?..... ☒ Yes ☐ No
  - Copy of Press Release or Talk Paper..... ☒

- Patent
  - Information [505(b)(1)] ..... ☒
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....

- Exclusivity Summary ..... ☒

- Debarment Statement ..... ☒

- Financial Disclosure
  - No disclosable information ..... ☒
  - Disclosable information – indicate where review is located .....

- Correspondence/Memoranda/Faxes ..... ☒

- Minutes of Meetings .....
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting February 08, 2000 ☒
  - Date of pre-AP Safety Conference _____

- Advisory Committee Meeting ..... N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....

- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... N/A

- Clinical review(s) and memoranda ..... ☒

Continued ⇨

- ♦ Safety Update review(s) ..... [X]
- ♦ Pediatric Information [X]
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... [X]
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted [X] Not Applicable
- ♦ Statistical review(s) and memoranda ..... [X]
- ♦ Biopharmaceutical review(s) and memoranda..... N/A
- ♦ Abuse Liability review(s) ..... N/A
  Recommendation for scheduling .....
- ♦ Microbiology (efficacy) review(s) and memoranda ..... N/A
- ♦ DSI Audits ..... N/A
  ☐Clinical studies ☐ bioequivalence studies .....

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- ♦ CMC review(s) and memoranda ..... [X]
- ♦ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A
- ♦ DMF review(s) ..... N/A
- ♦ Environmental Assessment review/FONSI/Categorical exemption ..... [X]
- ♦ Micro (validation of sterilization) review(s) and memoranda ..... N/A
- ♦ Facilities Inspection (include EES report) N/A
  Date completed _____ ..... ☐ Acceptable ☐ Not Acceptable
- ♦ Methods Validation ..... ☐ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- ♦ Pharm/Tox review(s) and memoranda ..... N/A
- ♦ Memo from DSI regarding GLP inspection (if any) ..... N/A

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-042 / SE1- 012 **and** NDA 21-052/ SE1- 007

Drugs: Vioxx (rofecoxib) Tablets 12.5 and 25 mg Applicant: Merck & Co., Inc.

Vioxx (rofecoxib) Suspension 12.5/5 and 25/5 mL

RPM Barbara Gould Phone 301 827-2090

☒ 505(b)(1)
☐505(b)(2) Reference listed drug

☐Fast Track ☐Rolling Review Review priority: ☒ S ☐P

Pivotal IND(s)

Application classifications:
Chem Class 1
Other (e.g., orphan, OTC)

PDUFA Goal Dates:
Primary January 01, 2002
Secondary March 01, 2002

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☒ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption
- Action Letter..... ☐AP ☒ AE ☐NA
- Labeling & Labels
  FDA revised labeling and reviews.....
  Original proposed labeling (package insert, patient package insert) .....
  Other labeling in class (most recent 3) or class labeling.....
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☐ No
  Immediate container and carton labels .....
  Nomenclature review .....
- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☒ is not on the AIP.
  Exception for review (Center Director's memo).....
  OC Clearance for approval.....

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☐ Materials requested in AP letter

- Post-marketing Commitments — N/A
  - Agency request for Phase 4 Commitments .....
  - Copy of Applicant's commitments .....

- Was Press Office notified of action (for approval action only)? ..... ☐ Yes ☒ No
  - Copy of Press Release or Talk Paper .....

- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)] .....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] .....

- Exclusivity Summary .....

- Debarment Statement X

- Financial Disclosure
  - No disclosable information X
  - Disclosable information – indicate where review is located .....

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings .....
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting February 08, 2000 X
  - Date of pre-AP Safety Conference _____

- Advisory Committee Meeting ..... N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....

- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... N/A

- Clinical review(s) and memoranda X

Continued ⇨

- ♦ Safety Update review(s) X

- ♦ Pediatric Information X
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... N/A
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☒ Not Applicable

- ♦ Statistical review(s) and memoranda X

- ♦ Biopharmaceutical review(s) and memoranda..... N/A

- ♦ Abuse Liability review(s) ..... N/A
  Recommendation for scheduling .....

- ♦ Microbiology (efficacy) review(s) and memoranda ..... N/A

- ♦ DSI Audits ..... N/A
  ☐Clinical studies ☐ bioequivalence studies .....

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ♦ CMC review(s) and memoranda X

- ♦ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A

- ♦ DMF review(s) ..... N/A

- ♦ Environmental Assessment review/FONSI/Categorical exemption X

- ♦ Micro (validation of sterilization) review(s) and memoranda ..... N/A

- ♦ Facilities Inspection (include EES report) N/A
  Date completed _____ ..... ☐ Acceptable ☐ Not Acceptable

- ♦ Methods Validation ..... ☐ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ♦ Pharm/Tox review(s) and memoranda ..... N/A

- ♦ Memo from DSI regarding GLP inspection (if any) ..... N/A

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-042 /SE8 - 007
NDA 21-052 /SE8 - 004 - Vioxx Suspension 12.5mg/5 mL and 25 mg/5 mL

Drug Vioxx (rofecoxib) Tablets, 12.5 mg, 25 mg, and 50 mg Applicant Merck & Co.

RPM Sandra Folkendt Phone 301 827-2090

X 505(b)(1)
☐505(b)(2) Reference listed drug

☐Fast Track ☐Rolling Review Review priority: X S ☐P

Pivotal IND(s) —

Application classifications:
Chem Class
Other (e.g., orphan, OTC)

PDUFA Goal Dates:
Primary 4/29/01
Secondary 4/29/01

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: **X** User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☐AP X AE ☐NA

- Labeling & Labels
  FDA revised labeling and reviews..... N/A
  Original proposed labeling (package insert, patient package insert) X
  Other labeling in class (most recent 3) or class labeling..... X
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) X No
  Immediate container and carton labels ..... N/A
  Nomenclature review ..... N/A

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is **X** is not on the AIP.
  Exception for review (Center Director's memo)..... _____
  OC Clearance for approval..... _____

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☐ Materials requested in AP letter

- Post-marketing Commitments — N/A
  - Agency request for Phase 4 Commitments..... N/A
  - Copy of Applicant's commitments ..... N/A

- Was Press Office notified of action (for approval action only)?..... ☐ Yes ☐ No
  - Copy of Press Release or Talk Paper.....

- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)]..... X
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....

- Exclusivity Summary ..... N/A

- Debarment Statement X

- Financial Disclosure
  - No disclosable information .....
  - Disclosable information – indicate where review is located ..... In medical review

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings .....
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting 4/10/00
  - Date of pre-AP Safety Conference _____

- Advisory Committee Meeting .....
  - Date of Meeting 2/8/01
  - Questions considered by the committee X
  - Minutes or 48-hour alert or pertinent section of transcript X

- Federal Register Notices, DESI documents X

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... N/A

- Clinical review(s) and memoranda X

Continued ⇨

- Safety Update review(s) X

- Pediatric Information
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... _____
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted **X** Not Applicable

- Statistical review(s) and memoranda X

- Biopharmaceutical review(s) and memoranda..... N/A

- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling ..... _____

- Microbiology (efficacy) review(s) and memoranda ..... N/A

- DSI Audits ..... N/A
  ☒Clinical studies ☐ bioequivalence studies X

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- CMC review(s) and memoranda ..... N/A

- Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A

- DMF review(s) ..... N/A

- Environmental Assessment review/FONSI/Categorical exemption ..... N/A – SE8

- Micro (validation of sterilization) review(s) and memoranda ..... N/A

- Facilities Inspection (include EES report)
  Date completed _____ ..... ☐ Acceptable ☐ Not Acceptable

- Methods Validation ..... ☐ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Pharm/Tox review(s) and memoranda ..... N/A

- Memo from DSI regarding GLP inspection (if any) ..... N/A

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

APPEARS THIS WAY
ON ORIGINAL

PATENT SUBMISSION FORM

Time Sensitive Patent Information pursuant to 21 C.F.R. §314.53 and/or
Patent Information pursuant to 21 C.F.R. §314.53 and §314.60
for
NDA # 21-042 and supplements S-001, S-002, S-003, S-004, S-006, S-007, S-008, S-009,

---

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: VIOXX™
- Active Ingredient(s): Rofecoxib
- Strength(s): 12.5mg, 25mg and 50mg
- Dosage Form(s): Tablet
- Date NDA Filed: 11/23/1998
- Date NDA Approved: 05/20/1999

A. This section should be completed for each individual patent

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

APPEARS THIS WAY
ON ORIGINAL

Expiration Date: 06/24/2013

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: US 5,691,374

Expiration Date: 05/18/2015

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 US 5,691,374

covers the composition, formulation and/or method of use of _____

(name of drug product). This product is:

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

  OR

- __ 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: 05/06/2017

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 Frosst Canada and 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.

Respectfully submitted,

By _____
Curtis C. Panzer
Attorney for Applicants

Merck & Co., Inc.
P.O. Box 2000 - RY60-30
Rahway, NJ 07065-0907
(732) 594- 3199

Date: June 20, 2001

A copy of the above information should be submitted to the FDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

In accordance with 21 C.F.R. §314.53(d)(4), the applicant shall submit two copies of each submission of patent information to:

Central Document Room
Center For Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parklawn Dr.
Rockville, MD 20857

APPEARS THIS WAY
ON ORIGINAL

IN DUPLICATE

(Rofecoxib Tablets)

ent Information

m 13

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

Active Ingredient	rofecoxib
Dosage(s)	12.5 mg, 25 mg and 50 mg
Trade Name	VIOXX™
Dosage Form	Tablet
Route of Administration	Oral
5. Applicant Firm Name	Merck Research Laboratories
6. NDA Number	21-042 and supplements S-001, S-002, S-003, S-004, S-006, S-007, S-008,S-009
7. oval Date	05/20/1999. Supplements are pending
8. Exclusivity	Five (5) years from May 20, 1999 (May 20 2004) and three (3) years from approval dates from pending supplements

APPEARS THIS WAY
ON ORIGINAL

9. Applicable Patent Numbers	5,474,995 Expiration Date: June 24, 2013 5,691,374 Expiration Date: May 18, 2015 6,063,811 Expiration Date: May 6, 2017

NDA 21-042: VIOXX™
(Rofecoxib Tablets)
Item 13: Patent Information

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1.	Active Ingredient	rofecoxib
2.	Strength	12.5 mg, 25 mg and 50 mg
3.	Trade Name	VIOXX™
4.	Dosage Form Route of Administration	Tablet Oral
5.	Applicant Firm Name	Merck Research Laboratories
6.	NDA Number	21-042 and supplements S-001, S-002, S-003, S-004, S-006, S-007, S-008, S-009 [ ]
7.	NDA Approval Date	05/20/1999. Supplements are pending
8.	Exclusivity-Date First ANDA Could be Submitted	Five (5) years from May 20, 1999 (May 20 2004) and three (3) years from approval dates from pending supplements
9.	Applicable Patent Number	5,474,995 Expiration Date: June 24, 2013 5,691,374 Expiration Date: November 25, 2017 6,063,811 Expiration Date: May 16, 2017

April 27, 2001

PATENT SUBMISSION FORM

Time Sensitive Patent Information pursuant to 21 C.F.R. §314.53 and/or
Patent Information pursuant to 21 C.F.R. §314.53 and §314.60
for
NDA # 21-042 and supplements S-001, S-002, S-003, S-004, S-006, S-007, S-008, S-009,

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: VIOXX™
- Active Ingredient(s): Rofecoxib
- Strength(s): 12.5mg, 25mg and 50mg
- Dosage Form(s): Tablet
- Date NDA Filed: 11/23/1998
- Date NDA Approved: 05/20/1999

A. This section should be completed for each individual patent

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

Expiration Date: 06/24/2013

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: US 5,691,374

Expiration Date: 11/25/2017

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 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 US 5,691,374

covers the composition, formulation and/or method of use of _____

(name of drug product). This product is:

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

  OR

- __ 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: 05/16/2017

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 Frosst Canada and 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.

Respectfully submitted,

By Curtis Panzer
Curtis C. Panzer
Attorney for Applicants

Merck & Co., Inc.
P.O. Box 2000 - RY60-30
Rahway, NJ 07065-0907
(732) 594- 3199

Date: april 27, 2001

A copy of the above information should be submitted to the FDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

In accordance with 21 C.F.R. §314.53(d)(4), the applicant shall submit two copies of each submission of patent information to:

Central Document Room
Center For Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parklawn Dr.
Rockville, MD 20857

APPEARS THIS WAY
ON ORIGINAL

IN DUPLICATE

Patent Submission Suggested Format

This form contains a format suggestion for submission of patent information for NDAs submitted under section 505 of the Federal Food Drug and Cosmetic Act. For more detailed information please refer to 21 C.F.R. 314.53.

Time Sensitive Patent Information

pursuant to 21 C.F.R. 314.53

for

NDA # 21-042 VIOXX™

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: VIOXX
- Active Ingredient(s): rofecoxib
- Strength(s): 12.5 mg and 25 mg
- Dosage Form: Tablet
- Approval Date:

A. This section should be completed for each individual patent

This format repeats to allow up to three patents. If there are additional patents, please copy and attach.

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

Expiration Date: June 24, 2013

Type of Patent--Indicate all that apply:

1. Drug Substance(Active Ingredient) X Y ___N
2. Drug Product(Composition/Formulation) X Y ___N
3. Method of Use X Y ___N

a. If patent claims method(s) of use, please specify approved method(s)of use or method(s) of use for which approval is being sought that are covered by patent: osteoarthritis

Name of Patent Owner: Merck Frosst Canada & Co.

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

U.S. Patent Number: 5,691,374

Expiration Date: November 25, 2017

Type of Patent--Indicate all that apply:

1. Drug Substance(Active Ingredient) X Y ___N
2. Drug Product(Composition/Formulation) ___Y X N
3. Method of Use ___Y X N

a. If patent claims method(s) of use, please specify approved method(s)of use or method(s) of use for which approval is being sought that are covered by patent:

Name of Patent Owner: Merck Frosst Canada & Co.

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

U.S. Patent Number:

Expiration Date:

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

a. If patent claims method(s) of use, please specify approved method(s)of use or method(s) of use for which approval is being sought that are covered by patent:_____

Name of Patent Owner:

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 any of the above listed patents have Composition/Formulation or Method of Use claims.

This format repeats to allow up to three patents. If there are additional patents, please copy and attach.

The undersigned declares that the above stated 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)

OR

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

The undersigned declares that the above stated United States Patent Number _____ covers the composition, formulation and/or method of use of _____(name of drug product). This product is:

- ___currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

OR

- ___the subject of this application for which approval is being sought.)

The undersigned declares that the above stated United States Patent Number _____ covers the composition, formulation and/or method of use of _____(name of drug product). This product is:

- ___currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

OR

- ___the subject of this application for which approval is being sought.)

Signed: Curtis C. Panzer
Date: Dec. 18, 1998
Title (optional): Assistant Counsel, Patents, Merck & Co., Inc.
Telephone Number (optional):

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the ***The Orange Book***,* a deskcopy should be submitted to:

Mailing address: **(US Mail)**

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane

Rockville, MD 20857

OR

Location address: (for FedX deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301)-594-6463

* - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the ***The Orange Book***.

Previous Page

APPEARS THIS WAY
ON ORIGINAL

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, 314)

Form Approved OMB No. 091[illegible]
Expiration Date: April 30, [illegible]
See OMB Statement on next page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Merck & Co., Inc.	12-23-98
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(610) 397-2944	(610) 397-2516

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

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-042

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

CHEMICAL/ BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5*H*)-furanone	MK-0966

DOSAGE FORM	STRENGTHS:	ROUTE OF ADMINISTRATION
Tablets	12.5 mg, 25 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
treatment of the signs and symptoms of osteoarthritis, relief of pain and treatment of primary dysmenorrhea

APPLICATION INFORMATION

APPLICATION TYPE
(Check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCED 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 ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Updated Patent Certification

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

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

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for the 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.

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

NDA 21-052: VIOXX™
(Rofecoxib Oral Suspension)
Item 13: Patent Information

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1.	Active Ingredient	rofecoxib
2.	Strength	12.5 mg/5mL and 25 mg/5mL
3.	Trade Name	VIOXX™
4.	Dosage Form Route of Administration	Suspension Oral
5.	Applicant Firm Name	Merck Research Laboratories
6.	NDA Number	21-052
7.	Approval Date	___ ___ ___
8.	Exclusivity-Date First ANDA Could be Submitted	to be determined
9.	Applicable patent Number*	5,474,995 Expiration Date: June 24, 2013 5,691,374 Expiration Date: November 25, 2017

Patent Submission Suggested Format

This DRAFT format is currently only available on CDERnet. It is expected to be made available on the CDER Homepage of the World Wide Web in the near future after final review from General Counsel and Federal Register notice is made.

This form contains a format suggestion for submission of patent information for NDAs submitted under section 505 of the Federal Food Drug and Cosmetic Act. For more detailed information please refer to 21 C.F.R. 314.53.

Time Sensitive Patent Information

pursuant to 21 C.F.R. 314.53

for

NDA # 21-052 VIOXX™

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: VIOXX
- Active Ingredient(s): rofecoxib
- Strength(s): 12.5 mg/5ml and 25 mg/5ml
- Dosage Form: oral suspension

A. This section should be completed for each individual patent

This format repeats to allow up to three patents. If there are additional patents, please copy and attach.

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

Expiration Date: June 24, 2013

Type of Patent—Indicate all that apply:

1. Drug Substance(Active Ingredient) X Y ___N
2. Drug Product(Composition/Formulation) X Y ___N
3. Method of Use X Y ___N

a. If patent claims method(s) of use, please specify approved method(s)of use or method(s) of use for which approval is being sought that are covered by patent osteoarthritis

Name of Patent Owner: Merck Frosst Canada, Inc.

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

U.S. Patent Number: 5,691,374

Expiration Date: November 25, 2017

Type of Patent—Indicate all that apply:

1. Drug Substance(Active Ingredient) X Y ___N
2. Drug Product(Composition/Formulation) ___Y X N
3. Method of Use ___Y X N

a. If patent claims method(s) of use, please specify approved method(s)of use or method(s) of use for which approval is being sought that are covered by patent_____

Name of Patent Owner: Merck Frosst Canada, Inc.

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

U.S. Patent Number:

Expiration Date:

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

a. If patent claims method(s) of use, please specify approved method(s)of use or method(s) of use for which approval is being sought that are covered by patent_____

Name of Patent Owner:

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 any of the above listed patents have Composition/Formulation or Method of Use claims.

This format repeats to allow up to three patents. If there are additional patents, please copy and attach.

The undersigned declares that the above stated 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)

OR

- _X_the subject of this application for which approval is being sought.)

The undersigned declares that the above stated United States Patent Number _____ covers the composition, formulation and/or method of use of _____(name of drug product). This product is:

- ___currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

OR

- ___the subject of this application for which approval is being sought.)

The undersigned declares that the above stated United States Patent Number _____ covers the composition, formulation and/or method of use of _____(name of drug product). This product is:

- ___currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

OR

- ___the subject of this application for which approval is being sought.)

Signed: Curtis C Panzer Curtis C. Panzer
Date: October 5, 1998
Title (optional): Assistant Counsel, Patents, Merck & Co., Inc.
Telephone Number (optional):

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the *The Orange Book*," a deskcopy should be submitted to:

Mailing address: (US Mail)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research

Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

OR

Location address: (for FedX deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301)-594-6463

* - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the ***The Orange Book***.

Previous Page

APPEARS THIS WAY
ON ORIGINAL

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

clinical endpoints for trials in heavily pretreated patients.

5. Comments on any additional considerations for clinical trials in treatment experienced pediatric patients.

These submissions should contain docket number 00N–1585, and they should be made to the Dockets Management Branch address provided previously in this document.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by January 4, 2001. Oral presentations from the public will be scheduled between approximately 1 p.m. and 2 p.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before January 4, 2001, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: December 18, 2000.

Linda A. Suydam,

Senior Associate Commissioner.

[FR Doc. 00–32889 Filed 12–26–00; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Antiviral Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Antiviral Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on January 10, 2001, 8:30 a.m. to 5:30 p.m.

Location: Holiday Inn, Versailles Ballroom, 8120 Wisconsin Ave., Bethesda, MD.

Contact Person: Tara P. Turner, Center for Drug Evaluation and Research (HFD–21), Food and Drug Administration, 5600 Fishers Lane (for express delivery 5630 Fishers Lane, rm. 1093), Rockville, MD 20857, 301–827–7001, e-mail: TurnerT@cder.fda.gov, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 12531. Please call the Information Line for up-to-date information on this meeting.

Agenda: The committee will discuss new drug application (NDA) 21–227, Cancidas™ (caspofungin) Injection, Merck Research Laboratories, indicated for treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by January 4, 2001. Oral presentations from the public will be scheduled between approximately 1 p.m. and 2 p.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before January 4, 2001, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

FDA regrets that it was unable to publish this notice 15 days prior to the January 10, 2001, meeting. Because the agency believes there is some urgency to bring these issues to public discussion and qualified members of the Antiviral Drugs Advisory Committee were available at this time, the Commissioner of Food and Drugs concluded that it was in the public interest to hold this meeting even if there was not sufficient time for the customary 15-day public notice.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: December 18, 2000.

Linda A. Suydam,

Senior Associate Commissioner.

[FR Doc. 00–32890 Filed 12–26–00; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Arthritis Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Arthritis Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on February 7, 8, and 9, 2001, 8 a.m. to 5 p.m.

Location: Holiday Inn, The Ballroom, Two Montgomery Village Ave., Gaithersburg, MD.

Contact: Kathleen R. Reedy or LaNise S. Giles, Center for Drug Evaluation and Research (HFD–21), Food and Drug Administration, 5600 Fishers Lane (for express delivery, 5630 Fishers Lane, rm. 1093), Rockville, MD 20857, 301–827–7001, FAX 301–827–6776, or e-mail reedyk@cder.fda.gov, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 12532. Please call the Information Line for up-to-date information on this meeting.

Agenda: On February 7, 2001, the committee will discuss new drug application (NDA) 20–998/S009, Celebrex® (celecoxib, G. D. Searle & Co.) approved for the treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis in adults. The discussion is for modification of the label based on the results of the CLASS Trial, a study of the incidence of significant upper gastrointestinal effects. On February 8, 2001, the committee will discuss NDA 21–042/S007, Vioxx™ (rofecoxib, Merck Research Laboratories) approved for the treatment of signs and symptoms of osteoarthritis and the management of acute pain. The discussion is for changes in the product label related to results of the VIGOR Trial concerning clinical gastrointestinal events. On February 9, 2001, the committee will discuss NDA 20–905/S006, Arava™ (leflunomide, Aventis) approved for the treatment of active rheumatoid arthritis. The discussion is for an indication to prevent disability as evidenced by improved physical function.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by January 30, 2001. Oral presentations from the public will be scheduled between approximately 11 and 11:30 a. m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before January 30, 2001, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: December 18, 2000.

Linda A. Suydam,

Senior Associate Commissioner.

[FR Doc. 00–32891 Filed 12–26–00; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants (Ranch Hand Advisory Committee); Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants (Ranch Hand Advisory Committee).

General Function of the Committee: To advise the Secretary and the Assistant Secretary for Health concerning its oversight of the conduct of the Ranch Hand study by the U.S. Air Force and provide scientific oversight of the Department of Veterans Affairs (VA) Army Chemical Corps Vietnam Veterans Health Study, and other studies in which the Secretary or the Assistant Secretary for Health believes involvement by the committee is desirable.

Date and Time: The meeting will be held on January 22, 2001, 1 p.m. to 4:30 p.m., January 23, 2001, 8:30 a.m. to 4:30 p.m., and January 24, 2001, 8:30 to 12 noon.

Location: Parklawn Bldg., 5600 Fishers Lane, conference room K, Rockville, MD.

Contact Person: Barbara J. Jewell, Food and Drug Administration, 5600 Fishers Lane, rm. 16–53, Rockville, MD 20857, 301–827–6696, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 12560. Please call the Information Line for up-to-date information on this meeting.

Agenda: The committee will provide final comments and recommendations on the scope of work for the physical examinations and final report preparation for the sixth and final round of the Air Force Health Study.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by January 10, 2001. Oral presentations from the public will be scheduled on January 22, 2001, between approximately 3 p.m. to 4 p.m. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before January 10, 2001, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: December 15, 2000.

Linda A. Suydam,

Senior Associate Commissioner.

[FR Doc. 00–33022 Filed 12–26–00; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Transmissible Spongiform Encephalopathies (TSE) Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). At least one portion of the meeting will be closed to the public.

Name of Committee: Transmissible Spongiform Encephalopathies (TSE) Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on January 18, 2001, 8:30 a.m. to 5:30 p.m. and January 19, 2001, 8:30 a.m. to 5:30 p.m.

Location: Holiday Inn, Versailles Ballrooms I and II, 8120 Wisconsin Ave., Bethesda, MD.

Contact Person: William Freas or Sheila D. Langford, Center for Biologics Evaluation and Research (HFM–71), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–0314, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area), code 12392. Please call the Information Line for up-to-date information on this meeting.

Agenda: On January 18, 2001, the committee will discuss whether recent information about new variant Creutzfeldt-Jakob disease (nvCJD) in France and bovine spongiform encephalopathy in France and other European countries suggests a need to reconsider FDA policies on suitability of blood donors who lived or traveled in those countries. In the afternoon, the committee will discuss the risks of Creutzfeldt-Jakob disease (CJD) and vCJD transmission by human cells, tissues and cellular and tissue-based products intended for implantation, transplantation, infusion, or transfer that are currently or proposed to be regulated by FDA, and the possible deferral of donors who have resided in the United Kingdom. On January 19, 2001, the committee will discuss issues related to deer and elk infected with or exposed to chronic wasting disease in the United States and potential for human exposure. In the afternoon, the committee will discuss whether a history of possible exposure to various animal transmissible spongiform encephalopathy agents should be considered by FDA in determining suitability of blood donors.

Procedure: On January 18, 2001, from 8:30 a.m. to 5 p.m. and January 19, 2001, from 8:30 a.m. to 5:30 p.m., the meeting is open to the public. Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by January 12, 2001. Oral presentations from the public will be scheduled between approximately 10:30

EXCLUSIVITY SUMMARY for NDAs# 21-042 & 21-052 SUPPL # 012 & 007

Trade Name: Vioxx Tablets 12.5 mg 25 mg 50mg/Vioxx Suspension 12.5mg/5 mL, 25 mg/5mL

Generic Name: rofecoxib

Applicant Name: Merck & Co., Inc. **HFD-550**

Approval Date: April 11, 2002

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 /_✔__/

   b) Is it an effectiveness supplement? YES /_✔__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? __1

   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 /_✔__/ 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 /___/ NO /__✔_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

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

YES /___/ 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 /_✔__/

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 /__✔_/

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 /_✔__/ NO /___/

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

NDA # **21-042** **rofecoxib**

NDA # **21-052** **rofecoxib**

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 /_✔__/ 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 /_✔__/ 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 /_✔__/

(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 /__✔_/

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 /_✔__/

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 # 096

Investigation #2, Study # 097

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 /_✔__/

Investigation #2 YES /___/ NO /__✔_/

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 /__✔_/

Investigation #2 YES /___/ NO /_✔__/

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 #__, Study # 096

Investigation #__, Study # 097

Investigation #__, Study #

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 # ——— YES /✔/	NO /___/ Explain:
Investigation #2	
IND # ——— YES /✔/	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 _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are 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: _____

_____

_____

Barbara Gould *April 11, 2002*
Signature of Preparer Date
Title: Project Manger

Lawrence Goldkind April 11, 2002
Deputy Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/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

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

/s/

Lawrence Goldkind
4/11/02 11:46:41 AM

APPEARS THIS WAY
ON ORIGINAL

Memo to file (3/12/02)
NDA 21-042/s007. VIOXX (rofecoxib).
Addendum

To: Lawrence Goldkind, M.D., Deputy Division Director, DAAODP

Through: James Witter, M.D., Ph. D., Team Leader, DAAODP

From: Maria Lourdes Villalba, M.D., Medical Officer

Re: Cardiovascular data in Alzheimer's studies

1) Background

In view of the cardiovascular findings in VIGOR, the FDA has been conducting a detailed review of all available data on cardiovascular thrombotic events in a placebo-controlled database of approximately 3,000 patients enrolled in — studies for the prevention of Alzheimer's disease.

The Alzheimer's studies were not designed to evaluate cardiovascular outcomes. However, the studies included an elderly population (mean age 75 years). Patients at high cardiovascular risk such as those with a recent history of myocardial infarction and stroke, and patients taking estrogen replacement therapy were excluded; duration of the studies was shorter than most CV studies. After enrollment was complete, patients identified as potential candidates for cardiovascular prophylaxis were started on low dose aspirin (approximately 6% of patients in each treatment arm). For a description of the studies the reader is referred to this MO review of the Complete Response to the Approvable letter of April 6, 2001, dated November 28, 2001. At the time of the safety update report (SUR) (July 2001) one study has been completed and analyzed (091) — — due to lack of efficacy in study 091 - and one is still ongoing (078). The cut-off date used for these analyses was March 2001. Exposure data are presented in Table 1.

2) Exposure data

Table 1. Alzheimer's studies. Exposure up to March 16, 2001.

	Rofecoxib 25 mg			Placebo		
	N	Pt/years at risk	Median duration (days)	N	Pt/years at risk	Median duration (days)
091(completed)	346	301	366	346	366	448
078 (ongoing)	721	996	520	729	1098	577
—	381	165	153	376	169	158.5
Total	1448	1461	355.5	1451	1634	421

Source: sponsor's tables. SUR and 2/29/02 response to request for information.

Reviewer's comment: exposure to rofecoxib was somewhat shorter as compared to placebo, particularly in studies 091 and 078.

3) Safety results: Deaths and cardiovascular events. (*For review of other AE's the reader is referred to this MO review of the Complete Response to the Approvable letter of April 6, 2001, dated November 28, 2001).*

1. Deaths

1.1 Total cause mortality

There were 33 and 20 deaths for all causes in the rofecoxib 25 and placebo groups respectively. If we consider the deaths from the long-term studies only (078 and 091), there were 29 and 15 deaths in the rofecoxib 25 mg and placebo group, respectively. Review of the causes of death did not suggest a particular pattern, with the possible exception of cardiovascular deaths, as noted below. (For a listing of causes of death the reader is referred to the MO review of 11/28/01.)

1.2 Cardiovascular deaths

Of all deaths, 10 and 6 were cardiovascular deaths (See Table 2) in the rofecoxib and placebo groups, respectively. CV deaths include sudden death, fatal MI or stroke – ischemic or hemorrhagic- and ruptured aortic aneurysm

Of the CV deaths, 8 and 4 were adjudicated as cardiovascular thrombotic deaths (by the CV adjudication committee) in the rofecoxib and placebo groups, respectively. By the time study [redacted], there were 4 deaths for all causes in each treatment group. Only one was cardiovascular thrombotic (a fatal MI in a patient who had meningitis in the placebo group.)

Table 2. Listing of Cardiovascular Mortality in Alzheimer's Studies.

Rofecoxib (n=10)	Placebo (n= 6)
Protocol 091	
332: acute MI (fatal)	784: sudden cardiac death
601: sudden cardiac death	*827 hemorrhagic stroke (fatal)
831: ischemic cerebrovascular stroke (fatal)	* 956 ruptured aortic aneurysm
Protocol 078	
248: sudden cardiac death	1256: sudden cardiac death
359: sudden cardiac death	1378: sudden cardiac death
737: sudden cardiac death	
799: sudden cardiac death	
1025: acute MI (fatal)	
[redacted]	
*532: hemorrhagic stroke (fatal)	661: acute MI (fatal)
*43: hemorrhagic stroke (fatal)	

* Hemorrhagic events were not "adjudicated" cardiovascular thrombotic events.

Reviewer's comment: although the numbers are small, the trend suggests more cardiovascular thrombotic deaths in the rofecoxib 25 mg daily group, as compared to placebo (8 vs. 4).

2. Serious Cardiovascular Thrombotic events (fatal and non-fatal)

The — studies included 156 cases of investigator reported serious CV thrombotic events referred for further evaluation by the CV adjudication committee. (Actually, these included cardiovascular cases within a list of pre-specified terms used by the sponsor in prior studies, as well as all deaths – cardiovascular and non-cardiovascular-).

Dr. Shari Targum, from the Division of Cardio-renal products (HFD-110) has conducted a blinded review of adjudication packages for all non-neurologic events referred for adjudication. There was no excess of CV thrombotic events – in particular no excess of myocardial infarction – in the rofecoxib group, upon her review of the data. (See review of December 2, 2001). The division of Neuropharm products (HFD-120) is conducting a similar, blinded review of cerebrovascular events, also in a blinded fashion.

Of note, twenty-two patients had non-neurologic, potential cardiovascular thrombotic events referred for adjudication, for which hospital or nursing home records were either not available or insufficient to adjudicate. Of those, 18 were receiving rofecoxib and 4 were receiving placebo. (Review of cerebrovascular events under review may reveal additional cases with insufficient information).

2.1 Adjudicated cardiac thrombotic events

The following table includes adjudicated cardiac thrombotic events from the long-term studies (078 and 091, median exposure: 14 months).

Table 3. Patients with adjudicated cardiac thrombotic events in studies 078 and 091*.

	Rofecoxib 25 mg					Placebo				
	Pt years risk	MI		SD	UA	Pt years risk	MI		SD	UA
		fatal	Non-fatal				fatal	Non-fatal		
091	301	1	1	1	0	366	0	4	1	1
078	966	1[1]	5	4	0	1098	0	7	2	4
Total	1267	8		5	0	1464	11[2]		3	5

Source: sponsor's table. SUR and 2/19/02 submission. *Median exposure: 14 months. N = randomized. MI: myocardial infarction. SD: sudden death. UA: unstable angina. Patients with more than one event are listed under the most serious event. [1]This patient also had unstable angina. [2] Three of these patients also had unstable angina.

Reviewer's comment: There was no excess of MI in the rofecoxib 25 mg daily group, as compared to the placebo group.

As noted above, there was an imbalance in the number of CV thrombotic cases referred for adjudication that had "insufficient information" in this database (18 and 4 in the rofecoxib and placebo groups, respectively). If we were to take into consideration those patients for which the investigator, the medical records or the FDA reviewer had entertained the diagnosis of a myocardial infarction but there was insufficient information, the numbers would still suggest no increased risk of MI in the rofecoxib 25 mg group as compared to placebo in this population.

2.2 Cerebrovascular and peripheral thrombotic events in Alzheimer's studies

Table 5. Patients with adjudicated cerebrovascular and peripheral events in study 078 and 091.

	N	TIA	Ischemic stroke	Arterial thromboses	Venous thromboses
Rofecoxib 25 mg	1267	3	3	0	0
Placebo	1464	2	12	1	2

N: patients randomized. Source: Adjudication packages from 7/12/01 submission and 9/19/02 submission.

Reviewer's comment: The numbers suggest an excess of cerebrovascular thrombotic events in the placebo group as compared to the rofecoxib group. This finding is difficult to interpret. Review of cases by the division of Neuropharm products is still ongoing.

3. Fluid retention, edema and hypertension

In the Alzheimer's studies, rofecoxib 25 mg daily was associated with increased incidence of fluid retention, edema and hypertension as compared to placebo. (See MO review of 11/28/01). These adverse events are known to occur with all NSAIDs and appear to be dose-related.

Table 6. Summary of HTN, edema and CHF-related events in Alzheimer's studies 091 and —— (crude rates).

	Rofecoxib 25 mg[1] N= 726 n (%)	Placebo[2] N= 722 N (%)
HTN-related	63 (8.7)	19 (2.6)
Edema-related	21 (2.9)	6 (0.8)
CHF-related	16 (2.2)	6 (0.8)

* Source NDA 21-042/s007 safety update report. Median duration for study 091: one year. Median duration for —— five months. Data from 078 not provided. [1] Nine patients discontinued rofecoxib therapy due to the above AE's (3 in each category). [2] One patient discontinued placebo due to a HTN- related event.

In the original NDA the 6-month OA database had the following incidence of hypertension-related events: rofecoxib 12.5 mg: 6 %; rofecoxib 25 mg: 7 %; rofecoxib 50 mg: 12 %; ibuprofen 800 mg TID: 5 % and diclofenac 750 mg BID: 3 %.

In the RA efficacy database (NDA s012), in the one-year studies, rofecoxib (both, 25 and 50 mg) was associated with two to three fold increase in the incidence of hypertension-related events as compared to naproxen (15% and 5%, respectively).

Reviewer's comment:

Although these are crude rates and none of the studies were designed to address safety questions, there is a suggestion that rofecoxib at doses recommended for chronic use may be associated with a higher incidence of HTN-related events than other NSAIDs. Prospective, long-term, parallel studies on hypertension related-events with different NSAIDs are not available.

4. Conclusions:

The Alzheimer's studies described in this memo were not specifically designed or powered to address CV outcomes. However, they provide a relatively large placebo-controlled database (rofecoxib N= 1267, placebo N= 1464), with a median exposure of 14 months and a substantial number of MI and cerebrovascular events for analysis.

In this database, there was no excess for *all* cardiovascular thrombotic events (cardiac, cerebrovascular and peripheral together) and particularly, no excess of MI in the rofecoxib 25 mg group, as compared to placebo. However, total cause mortality (29 vs. 15) and cardiovascular thrombotic deaths (8 and 3) trended against rofecoxib.

These data support the hypothesis that the excess of MI found with rofecoxib 50 mg in the VIGOR study - as well as the trends observed in the ADVANTAGE and the RA databases with the 25 mg dose relative to naproxen - may in part be explained by the lack of an anti-platelet effect of rofecoxib relative to naproxen. However, in addition, the biologically plausible pro-thrombotic effect and the known effects on fluid retention, edema and hypertension may play a role in the different cardiovascular safety profile of rofecoxib as compared to naproxen.

[ ]

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

/s/

Maria Villalba
3/12/02 11:34:47 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF CONSULTATION (Addendum to the Memorandum of March 14, 2002)

DATE: March 20, 2002

FROM: M. F. Huque, Ph.D.
Division of Biometrics III/OB/OPSS/CDER/
HFD-725

TO: Lawrence Goldkind, M.D.
Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products/
HFD-550

SUBJECT: Memorandum of March 14, 2002/
NDA 21-042/ Rofecoxib Labeling Comments

Documents Reviewed: 1) Merck draft of 15 Feb 2002
2) Merck "VIGOR Cardiovascular Hazard Rates Analysis"

This memorandum corrects a few typographical errors that were found in column (2) and (4) of Table 1 of the Naproxen group. This table was sent to you as an attachment of the memorandum of March 14, 2002. The new revised table is labeled as "Table 1 (Revised)" to distinguish it from the old table "Table 1". The old table however had correct hazard rate estimates, standard error of the estimates and confidence intervals for drawing statistical conclusions.

All my earlier comments and suggestions included in the March 14 memorandum hold and do not change.

Attachment:

Table 1 (Revised) gives hazard rate estimates for every 4-month intervals and confidence intervals for the cardiovascular events only, total 45 CV events for the Rofecoxib group and total 19 CV events for the Naproxen group.

cc:
HFD-550
HFD-550/Ms. Gould
HFD-550/Dr. Goldkind
HFD-725/Dr. Stan Lin
HFD-725/Dr. Qian Li
HFD-725/Dr. Huque
HFD-700/Dr. O'Neill
HFD-700/Dr. Anello

Table 1 (REVISED) : **Hazard Rate Estimates**
Cardiovascular Events Only (Rofecoxib 45 versus Naproxen 19)
(Data extracted from the sponsor's electronic data file)

Rofecoxib Group

By Every 4 Months	d= number of Events	Number censored	Effective Sample Size (n-w/2)	Patient-years at risk	h=hazard rate	SE(h)	h ± 2*SE
0-4	17	625	3734.5	1245	1.36%	0.3324	(0.69, 2.02)
4-8	12	587	3111.5	1037	1.16	0.3348	(0.49, 1.83)
8-12	16	2733	1439.5	480	3.35	0.8388	(1.67, 5.03)

Total 45 Events

Naproxen Group

By Every 4 Months	d= number of Events	Number censored	Effective Sample Size (n-w/2)	Patient-years at risk	h=hazard rate	SE(h)	h ± 2*SE
1-4	9	625	3716.5	1239	0.73%	0.2424	(0.25, 1.21)
4-8	6	591	3099.5	1033	0.58	0.2376	(0.10, 1.06)
8-12	4	2734	1431.0	477	0.84	0.4200	(0.00, 1.68)

Total 19 Events

MEMORANDUM OF CONSULTATION

DATE: March 14, 2002

FROM: M. F. Huque, Ph.D.
Division of Biometrics III/OB/OPSS/CDER/
HFD-725

TO: Lawrence Goldkind, M.D.
Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products/
HFD-550

SUBJECT: NDA 21-042/ Rofecoxib Labeling Comments

Documents Reviewed: 1) Merck draft of 15 Feb 2002
2) Merck "VIGOR Cardiovascular Hazard Rates Analysis"

I have done a few analyses of the VIGOR cardiovascular events data. The results are summarized in Tables 1 and 2, and in Figures 1 and 2. The Rofecoxib group tends to show different hazard rate pattern than the ~~~ group. This difference appears during the 8-12 month interval. The data cast doubt on the constant hazard rate assumption for the Rofecoxib group.

The above 2 tables and figures along with this memorandum document may be shared with the sponsor for them to consider the following:

1. Crude rates will not be appropriate because effective sample size decreases over time.
2. Incidence rate (per patient-years) calculations on assuming constant hazard rate for the Rofecoxib group for this data is hard to justify.

I suggest that the sponsor consider including following information regarding CV events in the revision of their draft-labeling document.

3. Twelve-month cumulative incidence rates, by treatment groups, for example, by the Kaplan-Meier or Life-Table method, along with the total number of events.
4. Graphical displays with respect to time, e.g., cumulative hazard rate plots, to convey total risk picture over time conveyed by the data, along with the log-rank test p-value for the between treatment comparison.
5. Relative risk estimate and confidence interval using Cox-regression, if convinced that the proportional hazard assumption is at least approximately valid. Otherwise, actuarial relative risk estimates and confidence intervals for appropriate time intervals, e.g., 4-month intervals.
6. Table 1 (p. 8) and Table 2 (p. 10) need to be similar in including the type of information.

Attachments:

Table 1 gives hazard rate estimates for every 4-month intervals and confidence intervals for the cardiovascular events only

Table 2 gives hazard rate estimates for every 4-month intervals and confidence intervals for all events (data extracted from the sponsor's Table 1 of the document "VIGOR Cardiovascular Hazard Rates Analysis."

Figure 1 gives cumulative hazard rate plot (also known as -log (S) plot) for the cardiovascular events only

Figure 2 gives hazard rate plot (unit is month). Multiply by 12 when reading this plot for hazard rate/year

cc:
HFD-550
HFD-550/Ms. Gould
HFD-550/Dr. Goldkind
HFD-725/Dr. Stan Lin
HFD-725/Dr. Qian Li
HFD-725/Dr. Huque
HFD-700/Dr. O'Neill
HFD-700/Dr. Anello

Table 1 : **Hazard Rate Estimates**
Cardiovascular Events Only (Rofecoxib 45 versus —— 19)
(Data extracted from the sponsor's electronic data file)

Rofecoxib Group

By Every 4 Months	d= number of Events	Number censored	Effective Sample Size (n-w/2)	Patient-years at risk	h=hazard rate	SE(h)	h ± 2*SE
0-4	17	625	3734.5	1245	1.36%	0.3324	(0.69, 2.02)
4-8	12	587	3111.5	1037	1.16	0.3348	(0.49, 1.83)
8-12	16	2733	1439.5	480	3.35	0.8388	(1.67, 5.03)

——n Group

By Every 4 Months	d= number of Events	Number censored	Effective Sample Size (n-w/2)	Patient-years at risk	h=hazard rate	SE(h)	h ± 2*SE
1-4		625	3716.5	1239	0.73%	0.2424	(0.25, 1.21)
4-8		591	1033.2	1033	0.58	0.2376	(0.10, 1.06)
8-12		2734	1431.0	477	0.84	0.4200	(0.00, 1.68)

Table 2 : **Hazard Rate Estimates**
Total events Rofecoxib 64 versus —— 32
(Data extracted from the sponsor's Table 1)

Rofecoxib Group

Months	d= number of Events	Patient-years at risk	h=hazard rate	SE(h)	h ± 2*SE
1-4	26	1232	2.13%	0.418	(1.30, 2.97)
4-8	17	1056	1.62	0.394	(0.84, 2.41)
> 8	21	407	5.30	1.156	(2.98, 7.61)*

*Non-overlapping interval with previous 2 intervals

—— Group

Months	d= number of Events	Patient-years at risk	h=hazard rate	SE(h)	h ± 2*SE
1-4	14	1231	1.144%	0.306	(0.53, 1.76)
4-8	12	1055	1.144	0.330	(0.48, 1.80)
> 8	6	410	1.474	0.602	(0.27, 2.68)**

** Overlapping interval with previous 2 intervals

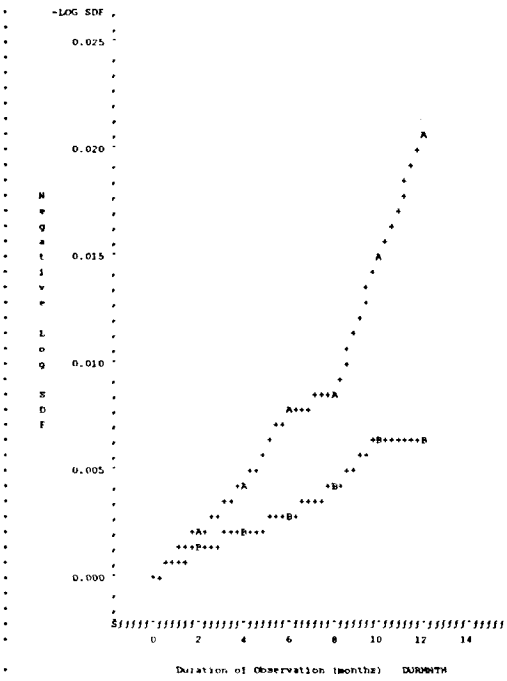
References for Computing Formulas:

1. Gehan's Large-sample Formula *1969 J. Chron. Dis. 21, 629-644*
2. SAS: PROC LIFETEST Program

Figures 1 and 2 are also included as power point documents

APPEARS THIS WAY
ON ORIGINAL

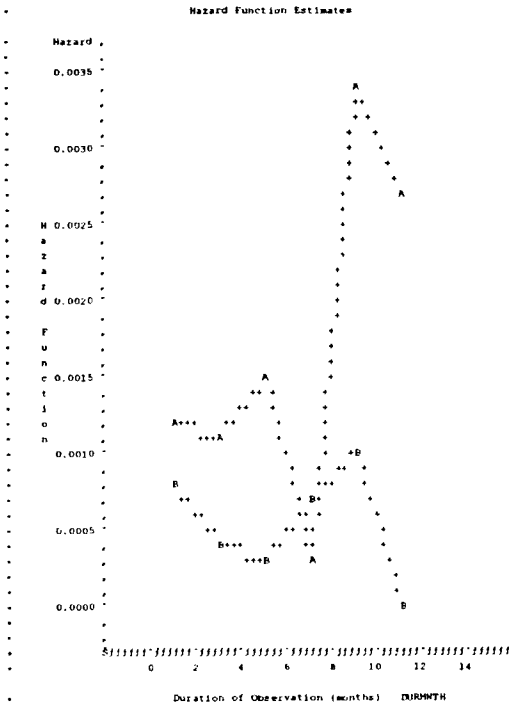
Figure 1: Plot of the Cumulative Hazard Function
-Log(Survival Function) Estimates
Cardiovascular Events Only (A, 45 events; B, 19 events)
(A=Vioxx 50 mg/day; B=~~~~ 1000 mg/day)



APPEARS THIS WAY
ON ORIGINAL

Figure 2.
Hazard Function Estimates

Cardiovascular Events Only (A. 45 events; B, 19 events)
(A=Vioxx 50 mg/day; B= ——→ 1000 mg/day)
(Note: The hazard rate in the rigure needs to be multiplied by 12 for the rate per year)



APPEARS THIS WAY
ON ORIGINAL

Figure 1: Plot of the Cumulative Hazard Function
-Log(Survival Function) Estimates
Cardiovascular Events Only (A, 45 events; B, 19 events)
(A=Vioxx 50 mg/day; B= ——— 1000 mg/day)

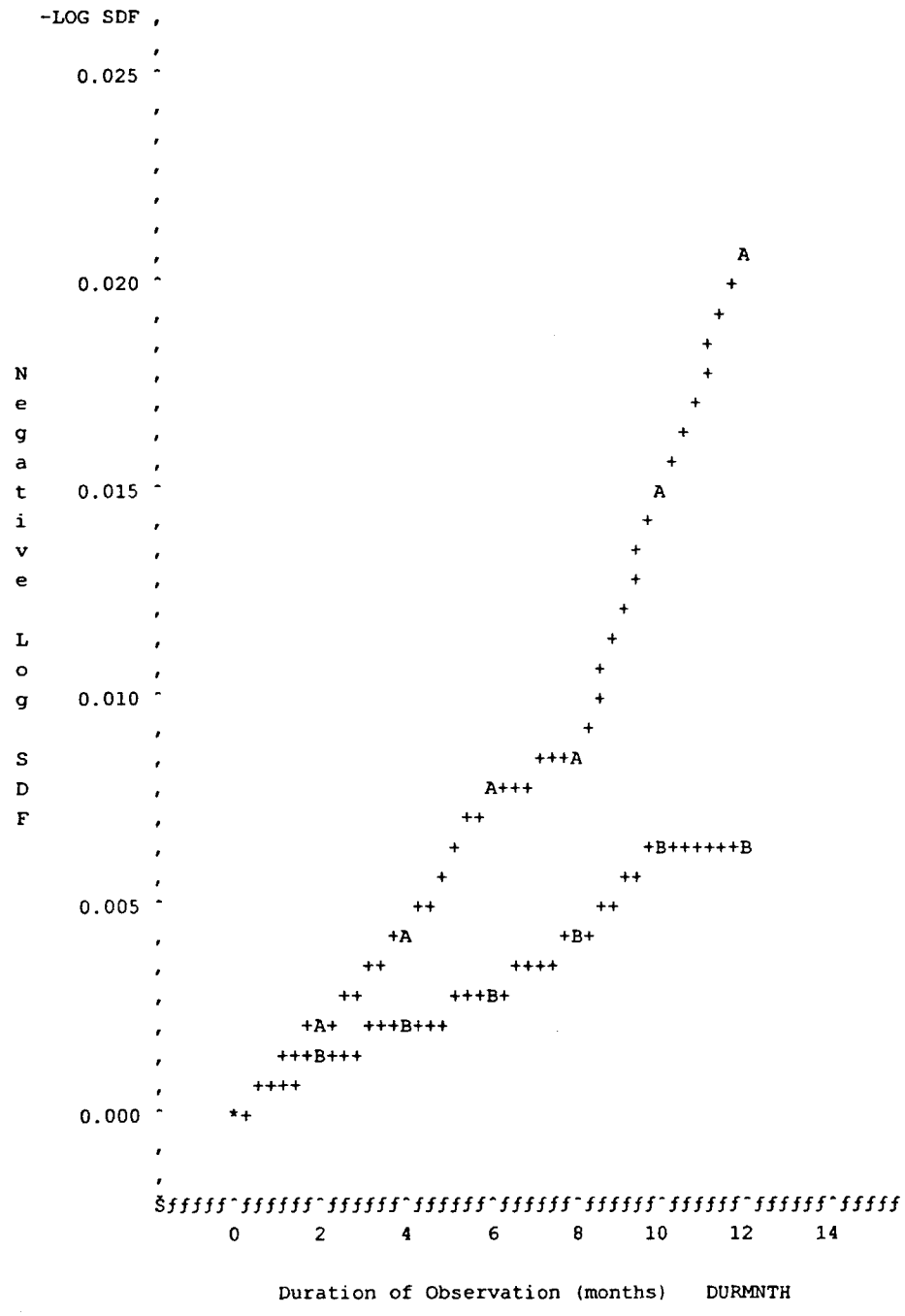


Figure 2:
Hazard Function Estimates

Cardiovascular Events Only (A, 45 events; B, 19 events)
(A=Vioxx 50 mg/day; B= ——— 1000 mg/day)
(Note: The hazard rate in the figure needs to be multiplied by 12 for the rate per year)