# 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**

# CORRESPONDENCE

# MEMORANDUM

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

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**Division of Neuropharmacological Drug Products (HFD-120)**
**Center for Drug Evaluation and Research**

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|---|---|
| Date: | September 28, 2001 |
| From: | Russell Katz, M.D., Division Director<br>Division of Neuropharmacological Drug Products, HFD-120 |
| Subject: | Case adjudication in the ADVANTAGE trial |
| To: | Dr. Villalba, HFD-550 |
| Document type: | Consultative Review |
| ODE1 number: | |

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See the attached review for the Division's comments.

APPEARS THIS WAY
ON ORIGINAL

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**Memorandum**

**DATE:** February 1, 2001

**FROM:** Shari L. Targum, M.D., Medical Officer
Division of Cardio-Renal Drug Products, HFD-110
**THROUGH:** Norman Stockbridge, M.D., Ph.D., Team Leader
Division of Cardio-Renal Drug Products, HFD-110
Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products, HFD-110
**TO:** Sandra Cook, Project Manager, Division of Anti-Inflammatory Drug Products, HFD-550
Maria L. Villalba, MD, Medical Officer, Division of Anti-Inflammatory Drug Products, HFD-550

**SUBJECT:** Consultation NDA 21-042, S-007
Review of cardiovascular safety database

**NAME OF DRUG:** Rofecoxib (MK-0966)
**TRADE NAME:** VIOXX™
**FORMULATION:** tablets

**RELATED APPLICATIONS:** A submission for efficacy in rheumatoid arthritis is planned for the end of 2000.
**APPROVED INDICATIONS:** Acute pain (50 mg/day for up to 5 days) and osteoarthritis (12.5 and 25 mg/day)
**SPONSOR:** MERCK Research Laboratories

**DOCUMENTS AVAILABLE FOR REVIEW:**
1. NDA 21-042, S-007 (electronic document room); 2. Prior Consultation from HFD-110 (Dr. Pelayo), 4/30/99;
3. Primary Medical Review (Dr. Villalba), NDA 21-042; 4. Rodriguez LA et. al: Differential Effects of Aspirin and Non-Aspirin Nonsteroidal Antiinflammatory Drugs in the Primary Prevention of Myocardial Infarction in Postmenopausal Women. *Epidemiology* 2000; 11 (4):382-387.

**DATE CONSULT RECEIVED:** August 16, 2000
**DATE CONSULT COMPLETED:** December 8, 2000

The purpose of this consultation is to address a concern regarding risk of cardiovascular events with the use of rofecoxib, a selective COX-2 inhibitor. The Medical Reviewer, HFD-550, had five specific questions (see Attached Consultation) for the Cardio-Renal Division; these questions will be addressed under Issues and Comments, page 30.

APPEARS THIS WAY
ON ORIGINAL

**BACKGROUND:**

Prostaglandins have a role in a wide variety of processes, including inflammation and pain; inhibition of prostaglandin production by cyclooxygenase (COX) inhibitors such as aspirin and nonsteroidal anti-inflammatory has been an important means of providing analgesic and anti-inflammatory benefits.

Cyclooxygenases, enzymes that metabolize arachidonic acid to produce prostaglandins, are subdivided into two isoforms:

1. COX-1, constitutively expressed in most cells, which results in the production of homeostatic prostaglandins that maintain GI mucosal integrity as well as renal blood flow ; in addition, COX-1, found in platelets, mediates production of thromboxane A2, a prostaglandin that promotes vasoconstriction and well as platelet activation and aggregation.

2. COX-2, purportedly inducible[1] in selected tissues, which results in the production of prostaglandins at inflammatory sites as well as prostacyclin ($PGI_2$), a vasodilator and inhibitor of platelet aggregation. Platelets do not express COX-2; COX-2 inhibition, therefore, would not be expected to directly affect platelet function. However, COX-2 inhibition might, by suppressing prostacyclin production, "inhibit the inhibitor" of platelet aggregation.

Selective COX-2 inhibition would thus have the theoretical benefit of analgesia and decreased inflammation with fewer GI-related side effects (decreased bleeding, ulcers); however, there would also exist a theoretical concern about PGI inhibition and unopposed thromboxane production, leading to an increase in cardiovascular thrombotic events.

Evidence for inhibition of prostacyclin but not thromboxane can be found in this sNDA (CV Events Analysis, pages 79-84; see also Appendix A), where the lack of COX-2 effects on bleeding time and ex vivo platelet aggregation are noted.

It should be noted that there may be aspirin effects, other than thromboxane A2 and/or prostacyclin effects, that might alter the atherosclerotic process. While prostaglandin (thromboxane A2) inhibition has been the major mechanism of aspirin's cardiovascular benefit, it has been proposed that aspirin may also act as an antioxidant, protecting LDL from oxidative modification and improving endothelial dysfunction in atherosclerotic vessels[2]. There are currently two marketed COX-2 inhibitors: celecoxib and rofecoxib. As mentioned above, rofecoxib is approved for osteoarthritis (12.5-25 mg per day) and acute pain (50 mg/day for up to 5 days). Doses of rofecoxib up to 500 mg have been studied in man[3]. However, most of the exposure for $\geq$ 6 months has been to 12.5 and 25 mg daily; according to a prior NDA review, 272 patients have received rofecoxib 50 mg daily for $\geq$ 6 months[3]; at doses of 25-50 mg per day, hypertension, edema, and increased serum creatinine have been noted[4] in a dose-dependent manner.

The Sponsor has submitted sNDA-007 with the apparent goal of establishing a GI safety claim, i.e., reduction in GI bleeding and ulcers, for rofecoxib. An sNDA for an efficacy claim in the treatment of rheumatoid arthritis is planned for the end of 2000.

**Methology:**

The focus of this review was on the cardiovascular safety of rofecoxib (MK-0966) 50 mg daily in patients with rheumatoid arthritis. To accomplish this review, the Medical Reviewer used the electronic version of the sNDA submission as well as prior reviews (see footnotes) for a reference database. Unless otherwise indicated, all analyses utilized will be taken from the Sponsor's analyses and have not been corroborated by statisticians from HFD-110.

On October 13, 2000, the sponsor submitted a safety update which included 11 additional patients referred for adjudication of cardiovascular serious adverse experiences after February 10, 2000, the prespecified cut-off date in the original safety report. Where possible, the Medical Reviewer will present data from the safety update rather than the original report.

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[1] According to a prior consult from HFD-110 (Dr. Pelayo), there may be constitutive expression of COX-2 in the kidney.

[2] Awtry EH and Loscalzo J. Aspirin. *Circulation*. 2000; 101: 1206-1218.

[3] Prior Medical Officer (Dr. Villalba) review; NDA 21-042/21-052 (5/17/99): Safety Review: page 74.

[3] vide supra.

[4] Prior consult from HFD-110 (Dr. Pelayo) to HFD-550, completed April 30, 1999.

***Protocol 088-04 VIGOR (VIOXX GI Outcomes Research)***

Title: A Double-Blind, Randomized, Stratified, Parallel-Group Study to Assess the Incidence of PUBs[5] During Chronic Treatment With MK-0966 or Naproxen in Patients With Rheumatoid Arthritis: U.S. Cohort. (VIGOR)

Study dates: January 6, 1999 (first patient in) - March 17, 2000 (last patient out)
Number of sites: 301 (multinational)

Primary Objectives:

1. To determine the relative risk of confirmed PUB (Perforation, Ulcers, Bleeding) in patients taking MK-0966 50 mg daily compared to patients in the group taking naproxen 1000 mg/day.
2. To study the safety and tolerability of MK-0966 in patients with rheumatoid arthritis.

Study Design:

This was a Phase III parallel-group, double-blind study conducted under in-house blinding procedures. There were 2 protocols, 088 (US) and 089 (multinational); however the study was conducted as a single study with a projected total of 7000 patients, with approximately 3500 from the U.S. Treatment duration was partially event-driven, i.e. determined by the need to observe at least 120 confirmed PUBs and and at least 40 confirmed complicated PUBs, or for the minimum duration of treatment to be 6 months, whichever came last.

Patients were eligible if they were 50 years or older with rheumatoid arthritis and felt to require NSAID therapy for at least 1 year; patients 40 to 49 years on chronic oral steroids were also eligible. Patients were stratified by a history of a peptic ulcer, upper GI bleeding or perforation versus those without this history.

**The use of low-dose aspirin was not allowed in this study; patients requiring aspirin for cardioprotection were excluded.** Other "cardiac-related" exclusions: angina or congestive heart failure with symptoms at rest or minimal activity, myocardial infarction or coronary bypass grafting within 1 year, stroke or transient ischemic attack within 2 years, uncontrolled hypertension.

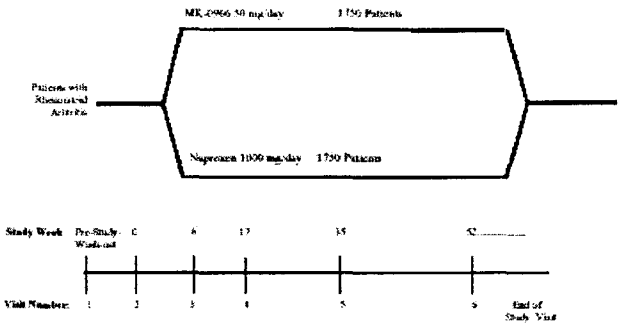
Those eligible were randomized to MK-0966 50 mg per day or naproxen 500 mg 2 times a day in a blinded fashion (double-dummy technique); there was no placebo arm. The primary endpoint was occurrence of PUBs. Other endpoints were related to efficacy or GI safety and included: complicated PUBs, discontinuation due to lack of efficacy, Patient Global Assessment of Disease Activity, and Investigator Global Assessment of Disease Activity.

Prespecified subgroups (for analysis) included: prior history of PUB, age, gender, race, and study region.



[5] **PUB** refers to gastrointestinal (GI) perforation, gastric outlet obstructions, complicated ulcers, severe upper GI bleeding.

STUDY DESIGN



Besides all serious adverse experiences and those leading to study discontinuation, prespecified adverse experiences included those related to: digestive system, hypertension, edema, renal (clinical or laboratory adverse experiences), hepatic (clinical or laboratory adverse experiences), and congestive heart failure;

Patients who discontinued were to have a discontinuation visit within 48 hours of their dropping from the study. In addition, those who discontinued were contacted 14 days after the last day of treatment for a safety follow-up. They were also contacted 45 days after the last day of treatment and at the end of study to specifically check for a GI adverse experience.

A Protocol Amendment on 9/2/99 removed the requirement for a 14 day follow up phone call for those completing the study.

Committees:

Steering Committee provided overall direction of the trial and was responsible for the trial's conduct. In the protocol, this committee was to be blinded to the results--though the DSMB (see below) had the option of "unblinding" some members of the Steering Committee to certain aspects of the data.

Executive Committee decided on practical issues during the trial and advised the Steering Committee.

Advisory Committee would meet with the DSMB, discuss recommendations to terminate the study or amend the protocol, and discuss these recommendations with the Steering Committee.

End Point Classification Committee was to define and review all PUBs (per protocol).

Case Review Committee was to have final blinded adjudication for all potential endpoints. This committee consisted of three voting clinicians, of whom at least two were gastroenterologists.

Data and Safety Monitoring Board (DSMB) monitored this trial for beneficial or adverse effects; except for a nonvoting Merck statistician, members of this committee were to be independent from the Sponsor, investigators, and patients.

A blinded, external Vascular Event Committee (VEC), containing three separate subspecialty committees (cardiac, cerebrovascular, and peripheral), existed for surveillance, monitoring, and adjudication of vascular events occurring in COX-2 inhibitor trials.

The Vascular Events Monitoring and Adjudication SOP can be found in the protocol: Category 3, Appendix 6 under 088c (sNDA, P088c: Appendix 3.2.1, pdf. Page 1681), dated August 30, 1999. Your Division, HFD-550, has been asked to clarify whether the Vascular Event Committee was prespecified, or created in response to a safety concern). The DSMB minutes begin in October, 1999.

DSMB: Minutes of the VIGOR DSMB meetings on October 4, 1999, November 18, 1999, and December 22, 1999 can be found in sNDA S-007: P088C: Appendix 3.9.1 (pdf pages 2937-2952).

The October 3, 1999 meeting was convened to discuss the first interim analysis of the VIGOR trial; at this time there was no specific mention of cardiovascular adverse events.

During the November 18, 1999 meeting, discussion focused on the "excess deaths and cardiovascular adverse experiences in Group A compared to Group B" (52 versus 29 serious cardiovascular events, respectively). In this report, there were 40 and 17 patients that discontinued the study because of cardiovascular adverse events in Groups A and B, respectively. In addition, a mean increase in systolic blood pressure ( 4 mm Hg) was noted in Group A and

a corresponding increase in hypertension adverse events, compared to little or no change in Group B. It was noted that this trial was unable to distinguish between a potentially harmful effect of Treatment A and a cardioprotective effect of Treatment B; in addition, the event rates were small. DSMB members expressed concern but the trial was allowed to continue. Additional analyses (Cox model, subdividing by those with underlying cardiac disease) were planned. An additional non-endpoint safety analysis was planned with a December 1 cutoff.

In a December 20, 1999 letter to the sponsor, the DSMB recommended development of a separate analysis plan for adjudicated events in the VIGOR study. This letter specifically stated that "it will be important that these events be adjudicated blinded." One concludes from this statement that the DSMB received unadjudicated adverse event data.

In the December 22, 1999 meeting the additional analysis was presented; it was noted that (as expected) a higher rate of events occurred in the higher risk patients in both treatment groups. No member felt that the trial should be stopped; members expressed belief that the effect might be "due to cardioprotective effects of Treatment B." At the time, no cardiovascular analysis plan was in place for VIGOR or VIOXX; it was again suggested that the analysis plan be developed prior to unblinding.

Results:

**Patient Disposition:**

The following table represents patient accounting, as noted by the sponsor. No meaningful differences in patient disposition are noted between the two treatment groups. Approximately 29% of patients did not complete this trial. The most common reason for discontinuation was the occurrence of a clinical adverse experience. There appear to be no meaningful differences between the two treatment groups in percentage discontinuing the trial and the overall reasons for discontinuation. Slightly more patients in the rofecoxib group were discontinued due to laboratory adverse experience and protocol deviations.

| | Patient Accounting | | | | | |
|---|---|---|---|---|---|---|
| | Rofecoxib 50 mg n (%) | | Naproxen 1000 mg n (%) | | Total n (%) | |
| TOTAL PATIENTS | 4047 (100.0) | | 4029 (100.0) | | 8076 (100.0) | |
| COMPLETED TRIAL | 2862 | (70.7) | 2880 | (71.5) | 5742 | (71.1) |
| DISCONTINUED TRIAL | 1185 | (29.3) | 1149 | (28.5) | 2334 | (28.9) |
| Clinical adverse experience | 645 | (15.9) | 636 | (15.8) | 1281 | (15.9) |
| Laboratory adverse experience | 22 | (0.5) | 12 | (0.3) | 34 | (0.4) |
| Lack efficacy | 256 | (6.3) | 263 | (6.5) | 519 | (6.4) |
| Lost to follow-up | 6 | (0.1) | 4 | (0.1) | 10 | (0.1) |
| Patient discontinued for other | 27 | (0.7) | 30 | (0.7) | 57 | (0.7) |
| Patient moved | 17 | (0.4) | 16 | (0.4) | 33 | (0.4) |
| Patient withdrew consent | 138 | (3.4) | 130 | (3.2) | 268 | (3.3) |
| Protocol deviation | 74 | (1.8) | 58 | (1.4) | 132 | (1.6) |
| Data Source: [4.7] | | | | | | |

(Source: Study Report 088c: pdf. page 92. Original submission: 6/29/00)

**Drug Exposure:**

As noted below, patients were followed for a mean of 8.0 months. There appear to be no meaningful differences in the two treatment groups in the duration of follow-up or the number of patients exposed to study drugs.
(Source: 088c Clinical study report pdf. page 93. Original submission: 6/29/00)

| Time in Study† | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Treatment | | | Duration of Follow-Up (Months) | | | |
| Cohort | Group | N | Mean | SD | Median | Range | Inter-Quartile Range |
| Overall | Rofecoxib | 4047 | 8.0 | 3.1 | 9.0 | 0.5 to 13.0 | 7.5 to 10.1 |
| | Naproxen | 4029 | 8.0 | 3.1 | 9.0 | 0.5 to 12.7 | 7.6 to 10.1 |
| | Total | 8076 | 8.0 | 3.1 | 9.0 | 0.5 to 13.0 | 7.6 to 10.1 |
| U.S. | Rofecoxib | 1748 | 7.5 | 3.6 | 8.5 | 0.5 to 13.0 | 4.4 to 10.3 |
| | Naproxen | 1750 | 7.5 | 3.5 | 8.5 | 0.5 to 12.7 | 4.4 to 10.3 |
| | Total | 3498 | 7.5 | 3.6 | 8.5 | 0.5 to 13.0 | 4.4 to 10.3 |
| Multi-national | Rofecoxib | 2299 | 8.4 | 2.7 | 9.2 | 0.5 to 12.3 | 8.0 to 10.0 |
| | Naproxen | 2279 | 8.4 | 2.6 | 9.2 | 0.5 to 12.2 | 8.1 to 10.0 |
| | Total | 4578 | 8.4 | 2.7 | 9.2 | 0.5 to 12.3 | 8.0 to 10.0 |
| † | Up to 14 days past discontinuation. | | | | | | |

| Number of Patients in the Study at Different Time Points† | | | | |
|---|---|---|---|---|
| | | Rofecoxib | Naproxen | Total |
| | | (N=4047) | (N=4029) | (N=8076) |
| Month | | n (%) | n (%) | n (%) |
| | 2 | 3645 (90.1) | 3647 (90.5) | 7292 (90.3) |
| | 4 | 3407 (84.2) | 3395 (84.3) | 6802 (84.2) |
| | 6 | 3181 (78.6) | 3173 (78.8) | 6354 (78.7) |
| | 8 | 2806 (69.3) | 2800 (69.5) | 5606 (69.4) |
| | 9 | 2026 (50.1) | 2039 (50.6) | 4065 (50.3) |
| | 10 | 1072 (26.5) | 1074 (26.7) | 2146 (26.6) |
| | 11 | 440 (10.9) | 432 (10.7) | 872 (10.8) |
| | 12 | 57 (1.4) | 60 (1.5) | 117 (1.4) |
| †The number of patients at each time point indicated represents the number of patients completing the previous time point and at risk at the beginning of the indicated time period. | | | | |
| Duration of observation includes 14 days past date of discontinuation. | | | | |
| (Source: 088c Study Report pdf. page 94. 6/29/00) | | | | |

**Baseline characteristics:**

Baseline characteristics between the two treatment groups revealed no meaningful differences in age, weight, height, ethnic group, study region, alcohol use, duration of RA, ARA status, smoking history, or history of cardiac disease.

The study population was mostly female (approx. 80%), mainly (over 70%) under 65, and mainly (approx. 68%) Caucasian. About 43% of the total population came from the U.S. Almost half of the total population had a history of "cardiac disease"(it is unclear how this parameter was defined) and about half had a history of any cardiac risk factor; however, less than 6% had a history of atherosclerotic cardiovascular disease (see below, Table C-1, Baseline Cardiovascular Demographics). About 82% had a history of prior NSAID use (for RA or other reasons) with no difference between the two treatment groups.

| Baseline Patient Characteristics by Treatment Group | | | |
|---|---|---|---|
| | | | |

| Treatment Group | N | Mean (SD) | |
|---|---|---|---|
| **Age (Years)** | | | |
| Rofecoxib | 4047 | 58.0 | (9.5) |
| Naproxen | 4029 | 58.2 | (9.6) |
| Total | 8076 | 58.1 | (9.5) |
| **Weight (kg)** | | | |
| Rofecoxib | 4045 | 72.2 | (17.7) |
| Naproxen | 4027 | 71.9 | (17.0) |
| Total | 8072 | 72.1 | (17.3) |
| **Height (cm)** | | | |
| Rofecoxib | 4026 | 161.8 | (10.2) |
| Naproxen | 4010 | 161.8 | (10.0) |
| Total | 8036 | 161.8 | (10.1) |

Source: Sponsor: 088c: pdf. page 98. Original submission 6/29/00.

| | Rofecoxib | | Naproxen | | Total | |
|---|---|---|---|---|---|---|
| Baseline Demographics | (N=4047) | | (N=4029) | | (N=8076) | |
| | n | (%) | n | (%) | n | (%) |
| **Gender** | | | | | | |
| Female | 3223 | (79.6) | 3215 | (79.8) | 6438 | (79.7) |
| Male | 824 | (20.4) | 814 | (20.2) | 1638 | (20.3) |
| **Ethnic Group** | | | | | | |
| White | 2761 | (68.2) | 2750 | (68.3) | 5511 | (68.2) |
| Black | 207 | (5.1) | 202 | (5.0) | 409 | (5.1) |
| Asian | 101 | (2.5) | 85 | (2.1) | 186 | (2.3) |
| Hispanic | 501 | (12.4) | 516 | (12.8) | 1017 | (12.6) |
| Multi-racial | 464 | (11.5) | 466 | (11.6) | 930 | (11.5) |
| Other | 13 | (0.3) | 10 | (0.2) | 23 | (0.3) |
| **Study Region** | | | | | | |
| U.S. | 1748 | (43.2) | 1750 | (43.4) | 3498 | (43.3) |
| Multinational | 2299 | (56.8) | 2279 | (56.6) | 4578 | (56.7) |
| **Age Group** | | | | | | |
| <40 | 10 | (0.2) | 11 | (0.3) | 21 | (0.3) |
| **History of Cardiac Disease** | | | | | | |
| Yes | 1884 | (46.6) | 1838 | (45.6) | 3722 | (46.1) |
| No | 2163 | (53.4) | 2191 | (54.4) | 4354 | (53.9) |
| **Smoking Status** | | | | | | |
| Unknown | 1 | (0.0) | 0 | (0.0) | 1 | (0.0) |
| Never Smoked | 2128 | (52.6) | 2150 | (53.4) | 4278 | (53.0) |
| Ex-Smoker | 1128 | (27.9) | 1100 | (27.3) | 2228 | (27.6) |
| Current Smoker | 790 | (19.5) | 779 | (19.3) | 1569 | (19.4) |
| **Number Cigarettes/24 Hours** | | | | | | |
| <11/day | 404 | (51.1) | 409 | (52.5) | 813 | (51.8) |
| 11 to 20/day | 271 | (34.3) | 252 | (32.3) | 523 | (33.3) |
| >20/day | 115 | (14.6) | 118 | (15.1) | 233 | (14.9) |

Source: 088c: pdf. Pages 99- 100. Original submission 6/29/00.

Baseline cardiac risk factors are presented ( next page):
There appear to be no meaningful differences between the two treatment groups in age, gender, past cardiovascular history, and cardiac risk factors.

| Baseline Cardiovascular Demographics in Rheumatoid Arthritis Patients | |
|---|---|

| Enrolled in the VIGOR Study | | | | |
|---|---|---|---|---|
| (CV events analysis: original table, 6/29/00) | | | | |
| | **Rofecoxib** | | **Naproxen** | |
| | (N=4047) | | (N=4029) | |
| Demographic | n | (%) | n | (%) |
| | | | | |
| **Age** | | | | |
| Percent <65 Years Old | 3050 | (75.4) | 2959 | (73.4) |
| Percent 65 Years Old | 997 | (24.6) | 1070 | (26.6) |
| **Past Cardiovascular History** | | | | |
| Past History of Atherosclerotic Cardiovascular Disease | 238 | (5.9) | 216 | (5.4) |
| Coronary Artery Disease | 171 | (4.2) | 153 | (3.8) |
| Myocardial Infarction | 57 | (1.4) | 50 | (1.2) |
| Cerebrovascular Disease | 26 | (0.6) | 25 | (0.6) |
| Cerebrovascular Accident | 12 | (0.3) | 16 | (0.4) |
| Peripheral Arterial Disease | 56 | (1.4) | 49 | (1.2) |
| **Cardiovascular Risk Factors** | | | | |
| Any Cardiovascular Risk Factor | 2047 | (50.6) | 1988 | (49.3) |
| Hypertension | 1217 | (30.1) | 1168 | (29.0) |
| Diabetes Mellitus | 240 | (5.9) | 254 | (6.3) |
| Current Smoker | 790 | (19.5) | 779 | (19.3) |
| Hypercholesterolemia | 343 | (8.5) | 293 | (7.3) |
| | | | | |
| **Indication for Aspirin Therapy** | | | | |
| Aspirin Therapy Indicated[†] | 170 | (4.2) | 151 | (3.7) |

[†] Patients with past medical histories that met criteria for chronic vascular-protective aspirin therapy (past history of either cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable or stable angina, coronary artery bypass graft surgery, or percutaneous coronary interventions).
[P088C]

In the October 13, 1999 Safety Update, the Baseline Cardiovascular Demographics were further subdivided by the sponsor into US and Multinational cohorts. This reviewer found no meaningful differences between the two treatment groups in the various baseline characteristics and cardiac risk factors. These tables can be found in S-007, 10-13-2000 Safety Update Report, Attachment 5, pdf. Pages 58-59.

Dropouts:

There were 1131 and 1032 patients in the rofecoxib and naproxen groups, respectively, that discontinued the study for any reason other than the primary endpoint. The rates of discontinuation were 42.6 and 38.9 per 100 patients years, respectively. The relative risk was 1.10 (95% CI: 1.01, 1.19; p=0.033). This difference appears to be due to an increase in discontinuations due to clinical adverse experiences other than PUBs.

The findings below are consistent with a previous safety review from HFD-110 which found a dose-related increase in hypertension and edema in rofecoxib.[6] There is a numerical increase in congestive heart failure adverse experiences in the rofecoxib group; this trend was not significant. It is unclear whether this trend (or this patient population) is related to, or is separate from, the edema-related adverse experiences. It is also unclear whether the congestive heart failure is related to other events, such as hypertension or ischemia. The sponsor should be asked to clarify these respective points.

| Analysis of Prespecified Adverse Experience (AE) Categories | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Patients | | | | | |
| | Treatment | | With | | | | Relative Risk[§] | |
| Type of Adverse Experience | Group | N | Events | PYR[†] | Rates[‡] | Estimate | 95% CI[%] | p-Value |
| Serious clinical AEs | Rofecoxib | 4047 | 378 | 2611 | 14.48 | 1.21 | (1.04, 1.40) | 0.013 |
| | Naproxen | 4029 | 315 | 2631 | 11.97 | | | |
| Clinical AEs leading to discontinuation | Rofecoxib | 4047 | 643 | 2649 | 24.27 | 1.01 | (0.91, 1.13) | 0.842 |
| | Naproxen | 4029 | 635 | 2647 | 23.99 | | | |
| Discontinues due to GI AEs + abdominal pain | Rofecoxib | 4047 | 307 | 2676 | 11.47 | 0.73 | (0.63, 0.85) | <0.001 |
| | Naproxen | 4029 | 416 | 2664 | 15.62 | | | |
| Discontinues due to edema-related AEs | Rofecoxib | 4047 | 25 | 2697 | 0.93 | 1.92 | (0.98, 3.75) | 0.057 |
| | Naproxen | 4029 | 13 | 2698 | 0.48 | | | |
| Discontinues due to hypertension-related AEs | Rofecoxib | 4047 | 28 | 2697 | 1.04 | 4.67 | (1.93, 11.28) | <0.001 |
| | Naproxen | 4029 | 6 | 2699 | 0.22 | | | |
| CHF AEs | Rofecoxib | 4047 | 19 | 2696 | 0.70 | 2.11 | (0.96, 4.67) | 0.065 |
| | Naproxen | 4029 | 9 | 2698 | 0.33 | | | |

[†] Patient-years at risk.

[‡] Per 100 PYR.

[§] Relative risk of rofecoxib with respect to naproxen from Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates and
p-value is from discrete log-rank
distribution.

[%] Confidence interval.

Data Source: [4.3]

Adapted from 088c: Table 44. pdf. Pages 152-153. Original submission 6/29/00.



[6] See prior consult from HFD-110 (Dr. Pelayo) to HFD-550, completed April 30, 1999.

**Adjudication:**

| Summary of Analysis of Cardiovascular Serious Adverse Experiences Referred for Adjudication | | | | | | | |
|---|---|---|---|---|---|---|---|
| VIGOR Study in Patients With Rheumatoid Arthritis (10/13/00 Safety Update) | | | | | | | |
| | Updated Application Data | | | | | | |
| | Treatment | | Patients With | | | Relative Risk | |
| Event Category | Group | N | Events | PYR[†] | Rates[‡] | Estimate | 95% CI |
| All unadjudicated thrombotic cardiovascular | Rofecoxib | 4047 | 64 | 2695 | 2.37 | | |
| serious adverse experiences | Naproxen | 4029 | 32 | 2696 | 1.19 | 0.50 | (0.33, 0.76) |
| [†] Patient-years at risk. | | | | | | | |
| [‡] Per 100 PYR. | | | | | | | |
| Data Source: [Attachment 3] | | | | | | | |

Serious adverse events were evaluated by an Independent Adjudication Committee. The following table shows a disposition of those events: (Source: Safety Update 10/13/2000: pdf. page 8)

| Table 1 | | |
|---|---|---|
| | | |
| Accounting of Cardiovascular Serious Adverse Experiences That Underwent | | |
| Adjudication in the VIGOR Trial in Rheumatoid Arthritis Patients | | |
| Updated Application Data | | |
| | | |
| Serious Adverse Experience Categories | Rofecoxib | Naproxen |
| | | |
| Serious adverse experiences meeting criteria for referral to | 65 | 33 |
| adjudication | | |
| Events not meeting criteria for a thrombotic cardiovascular serious | 19 | 13 |
| adverse experience | | |
| Events adjudicated to be nonthrombotic serious adverse | 12 | 9 |
| experiences | | |
| Events adjudicated to be hemorrhagic strokes or primary | 2 | 1 |
| intracranial hemorrhage events | | |
| Events with insufficient data for adjudication | 5 | 3 |
| Events meeting criteria for a thrombotic cardiovascular serious | 46 | 20 |
| adverse experience | | |

The events excluded from adjudication appear to have been balanced; there were still about twice as many events in the rofecoxib group than in the naproxen group, whether unadjudicated or adjudicated.

The SOP for the vascular event monitoring and adjudication can be found in 088c: Category 3: Appendix 3.2.1(pdf. Pages 1678-1691. Original submission 6/29/00). The criteria for vascular event adjudication were reviewed; coronary events referred for adjudication included myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, and sudden or unexplained death. Cerebrovascular events included stroke (ischemic and hemorrhagic) and transient ischemic attack. Also considered for adjudication were venous thrombosis and pulmonary embolism.

Adjudication guidelines (088c: Appendix H: pdf. Pages 1714-1717) for myocardial infarction include 1. new pathologic Q waves in 2 contiguous leads; or 2. ischemic symptoms or ischemic repolarization changes with rising cardiac enzymes. In patients undergoing invasive cardiac revascularization, criteria are: 1. Rise in CPK-MB; or 2. Rise in Cardiac Troponin I or T; or 3. Rise in CPK (in the absence of CPK-MB); in patients following CABG, new pathologic Q waves in 2 contiguous leads within 48 hours of the procedure (otherwise the criteria are the same as for those not undergoing invasive procedures).

These criteria for myocardial infarction appear to be acceptable to this Medical Reviewer.

**Safety:**

The approach used in the cardiovascular safety evaluation for the VIGOR study included: examination of deaths, discontinuations, serious adverse events, and treatment emergent adverse events.

**Discontinuations due to serious cardiovascular adverse experiences:**

The following table lists discontinuations due to serious adverse experiences. Presumably (given the numbers) these events were unadjudicated.

| Number (%) of Patients Discontinued Due to Specific Serious Clinical Adverse Experiences by Body System (Incidence _0.2% in One or More Treatment Groups) | | | | |
|---|---|---|---|---|
| | Rofecoxib (N=4047) | | Naproxen (N=4029) | |
| | n | (%) | n | (%) |
| Patients with one or more adverse experience | 143 | (3.5) | 127 | (3.2) |
| Patients with no adverse experience | 3904 | (96.5) | 3902 | (96.8) |
| Cardiovascular System | 61 | (1.5) | 21 | (0.5) |
| Cerebrovascular Accident | 10 | (0.2) | 3 | (0.1) |
| Myocardial Infarction | 12 | (0.3) | 3 | (0.1) |
| Digestive System | 27 | (0.7) | 61 | (1.5) |
| Gastric Ulcer | 2 | (0.0) | 11 | (0.3) |
| Hemorrhagic Duodenal Ulcer | 4 | (0.1) | 7 | (0.2) |
| Hemorrhagic Gastric Ulcer | 2 | (0.0) | 13 | (0.3) |
| Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories. | | | | |
| Data Source: [4.3; 4.17] | | | | |

Source: Adapted from 088: Table 58: pdf. page 196. Original submission 6/29/00.

Dizziness (0.5 versus 0.2%), congestive heart failure (0.1 versus 0.0%), hypertension (0.6 versus 0.1%), myocardial infarction (0.3 versus 0.1%), unstable angina (0.1 versus 0.0%), all led to study discontinuation more frequently with rofecoxib compared with naproxen.

The following is the sponsor's analysis using standard composite endpoints seen in antiplatelet trials. The sponsor has further subdivided patients into "aspirin indicated," those with conditions where low-dose aspirin for cardioprotection was indicated, and "aspirin not indicated" categories.

It can be seen that, in the "All Patients" category, there is an increased rate of MI and stroke in the rofecoxib group compared with naproxen; in the MI group, the 95% confidence interval is significant. In the two subgroups, the composite endpoint and MI events are still favorable for naproxen and unfavorable for rofecoxib.

This analysis could lead one to conclude that naproxen, with a 51% risk reduction compared to rofecoxib, would be the preferred drug.

**Analyses of Cardiovascular Events in the VIGOR Study Using Endpoint Definitions Standard in Large Antiplatelet Trials**

Updated Application Report (Safety Update: Table C-11: pdf. Pages 30-31) 10/13/00.

| | Treatment | | Number of Patients | | | Relative Risk[§] | | |
|---|---|---|---|---|---|---|---|---|
| Event Category | Group | N | With Events | PYR[†] | Rates[‡] | Estimate | 95% CI | |
| | | | | | | | | |
| **All Patients** | | | | | | | | |
| Cardiovascular deaths[%], MI, CVA | Rofecoxib | 4047 | 35 | 2698 | 1.30 | | | |
| | Naproxen | 4029 | 18 | 2698 | 0.67 | 0.51 | (0.29, | 0.91) |
| Cardiovascular deaths[%] | Rofecoxib | 4047 | 7 | 2700 | 0.26 | | | |
| | Naproxen | 4029 | 7 | 2699 | 0.26 | 1.00 | (0.35, | 2.85) |
| MI | Rofecoxib | 4047 | 20 | 2699 | 0.74 | | | |
| | Naproxen | 4029 | 4 | 2699 | 0.15 | 0.20 | (0.07, | 0.58) |
| Stroke[¶] | Rofecoxib | 4047 | 11 | 2699 | 0.41 | | | |
| | Naproxen | 4029 | 9 | 2699 | 0.33 | 0.82 | (0.34, | 1.97) |
| | | | | | | | | |
| **Aspirin Indicated** | | | | | | | | |
| Cardiovascular deaths[%], MI, CVA | Rofecoxib | 170 | 12 | 105 | 11.42 | | | |
| | Naproxen | 151 | 3 | 102 | 2.94 | 0.26 | (0.07, | 0.91) |
| Cardiovascular deaths[%] | Rofecoxib | 170 | 1 | 106 | 0.95 | | | |
| | Naproxen | 151 | 2 | 102 | 1.96 | 2.07 | (0.11, 122.10) | |
| MI | Rofecoxib | 170 | 8 | 105 | 7.60 | | | |
| | Naproxen | 151 | 0 | 102 | 0.00 | 0.00 | (0.00, | 0.60) |
| Stroke[¶] | Rofecoxib | 170 | 3 | 106 | 2.84 | | | |
| | Naproxen | 151 | 2 | 102 | 1.96 | 0.69 | (0.06, | 6.02) |

| Event Category | Treatment Group | N | Number of Patients | PYR | Rates | Relative Risk Estimate | 95% CI | |
|---|---|---|---|---|---|---|---|---|
| **Aspirin Not Indicated** | | | | | | | | |
| Cardiovascular deaths[%], MI, CVA | Rofecoxib | 3877 | 23 | 2593 | 0.89 | | | |
| | Naproxen | 3878 | 15 | 2596 | 0.58 | 0.65 | (0.34, | 1.25) |
| Cardiovascular deaths[%] | Rofecoxib | 3877 | 6 | 2594 | 0.23 | | | |
| | Naproxen | 3878 | 5 | 2597 | 0.19 | 0.83 | (0.25, | 2.73) |
| MI | Rofecoxib | 3877 | 12 | 2593 | 0.46 | | | |
| | Naproxen | 3878 | 4 | 2597 | 0.15 | 0.33 | (0.11, | 1.03) |
| Stroke¶ | Rofecoxib | 3877 | 8 | 2593 | 0.31 | | | |
| | Naproxen | 3878 | 7 | 2597 | 0.27 | 0.87 | (.32, | 2.40) |

† Patient-years at risk.

‡ Per 100 PYR.

§ Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.

% Includes sudden death, unknown cause of death, fatal myocardial infarction, fatal stroke (hemorrhagic or ischemic), fatal subarachnoid hemorrhage, fatal primary intracranial hemorrhage, fatal gastrointestinal bleeding episode.

¶ Includes fatal and nonfatal ischemic strokes, and fatal or nonfatal hemorrhagic strokes.

§ Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.

% Includes sudden death, unknown cause of death, fatal myocardial infarction, fatal stroke (hemorrhagic or ischemic), fatal subarachnoid hemorrhage, fatal primary intracranial hemorrhage, fatal GI bleeding episode.

¶ Includes fatal or nonfatal ischemic strokes, and fatal or nonfatal hemorrhagic strokes.

# "Aspirin Indicated" patients are patients with past medical histories of cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, angina pectoris, coronary artery bypass graft surgery, or percutaneous coronary interventions). [84] "Aspirin Not Indicated" patients are patients without a past medical history of these conditions.

[Attachment 3]

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**Serious Cardiovascular Adverse Experiences**

The following table was sent in a 10/13/00 safety update and represents confirmed adjudicated cardiovascular serious adverse experiences, as presented by the sponsor.

Of the breakdown of thrombotic events, it is the cardiac events which are significantly different (i.e., the Confidence Interval does not cross 1.0). It should be noted that the other categories have a smaller number of events but show consistently higher numbers of events, rates, and relative risk estimates in the rofecoxib group.

Summary of Analysis of Confirmed Adjudicated Thrombotic Cardiovascular Serious Adverse Experiences VIGOR Study in Patients With Rheumatoid Arthritis †

Updated Application
Data (10/13/00)

| | | Treatment | | Patients With | | | Relative Risk§ | |
|---|---|---|---|---|---|---|---|---|
| | Event Category | Group | N | Events | PYR‡ | Rates‡ | Estimate | 95% CI |
| All thrombotic events | | Rofecoxib | 4047 | 45 | 2697 | 1.67 | | |
| | | Naproxen | 4029 | 19 | 2698 | 0.70 | 0.42 | (0.25, 0.72) |
| All cardiac events | | Rofecoxib | 4047 | 28 | 2698 | 1.04 | | |
| | | Naproxen | 4029 | 10 | 2698 | 0.37 | 0.36 | (0.17, 0.74) |
| All cerebrovascular events | | Rofecoxib | 4047 | 11 | 2699 | 0.41 | | |
| | | Naproxen | 4029 | 8 | 2699 | 0.30 | 0.73 | (0.29, 1.80) |
| All peripheral vascular events | | Rofecoxib | 4047 | 6 | 2699 | 0.22 | | |
| | | Naproxen | 4029 | 1 | 2699 | 0.04 | 0.17 | (0.00, 1.37) |

† In keeping with the data analysis section of the Adjudication SOP, this table does not include events determined by adjudication to be hemorrhagic cerebrovascular accidents.

‡ Per 100 patient-years at risk (PYR).

§ Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.

Although a patient may have had 2 or more serious adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
Data Source: [Attachment 3]

**Time to Event**: The Time-to-Event Curves for Unconfirmed and Confirmed Thrombotic Events are shown.; the curves are similar in that they begin to diverge after about 6-8 weeks. It would be helpful to further analyze these curves for differences in these two groups. In addition, what event rates would be needed to show a significant difference between rofecoxib and naproxen? Both of these graphs are taken from the 10/13/00 safety update.

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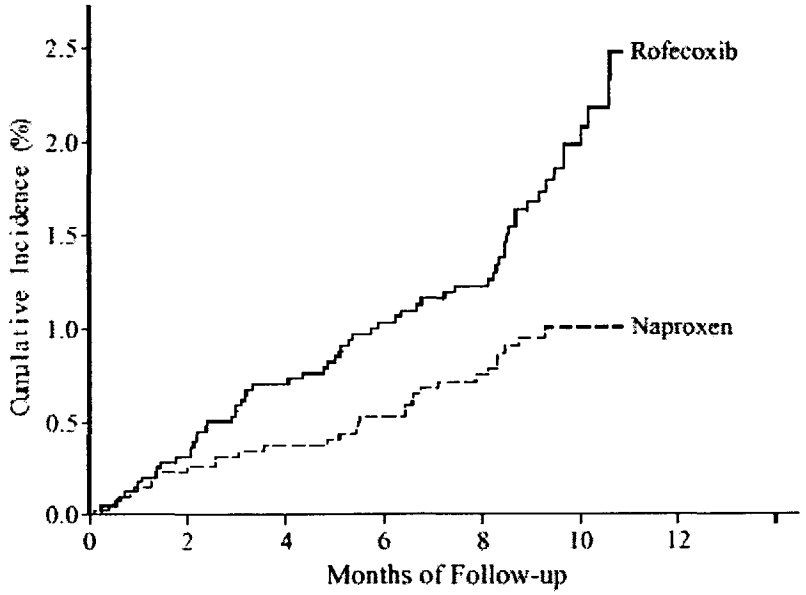
Figure 3

Thrombotic Cardiovascular Serious Adverse Experiences Referred for Adjudication in Rheumatoid Arthritis Patients in the VIGOR Study
Time-to-Event Plot (All Patients Randomized)
Updated Application Data




| # at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Rofecoxib | n=4047 | 3642 | 3403 | 3175 | 2804 | 1066 530 |
| Naproxen | n=4029 | 3646 | 3393 | 3169 | 2794 | 1071 513 |

(Source: 10/13/00 Safety Update: Figure 3: pdf. page 41)

On the next page, the time-to-event for Confirmed Cardiovascular Thrombotic Events is shown. (Source: Safety Update Figure 1: pdf. Page 15)

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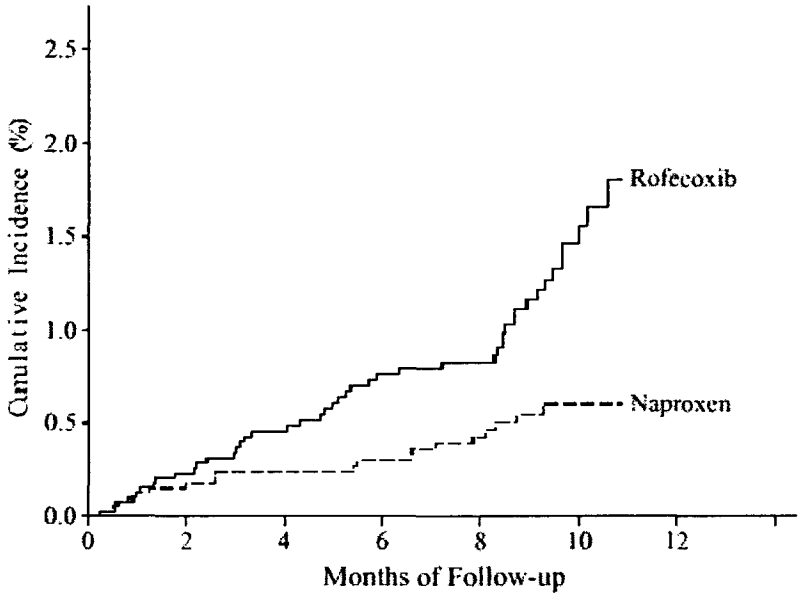
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
in Rheumatoid Arthritis Patients in the VIGOR Study
Time-to-Event Plot (All Patients Randomized)
Updated Application Data




| # at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Rofecoxib | n=4047 | 3643 | 3405 | 3177 | 2806 | 1067 531 |
| Naproxen | n=4029 | 3647 | 3395 | 3172 | 2798 | 1073 514 |

Data Source: [P088C], [Attachment 3]

**Adjudicated Thrombotic Serious Cardiovascular Adverse Experiences–Specific Events**

The following table lists adjudicated cardiovascular serious adverse experiences in the VIGOR Study. From this table it appears that the most striking difference between the two groups is under Myocardial Infarction (safety update 10/13/00) Please note that these are the sponsor's data. This Medical Reviewer counted at least 8 potential cardiac deaths in the rofecoxib group (see Deaths, next page). Also, hemorrhagic stroke, which may not be thrombotic, is included.

| Summary of Adjudicated Thrombotic Cardiovascular Serious Adverse Experiences VIGOR Study in Patients With Rheumatoid Arthritis Updated Application Data | | | | |
|---|---|---|---|---|
| | Rofecoxib (N=4047) | | Naproxen (N=4029) | |
| Event | n | (%) | n | (%) |
| **Any Event†** | **47** | **(1.2)** | **20** | **(0.5)** |
| **Arterial Event†** | **42** | **(1.0)** | **19** | **(0.5)** |
| Venous Event | 5 | (0.1) | 1 | (0.0) |
| Cardiovascular Death† | 6 | (0.1) | 6 | (0.1) |
| Fatal Acute Myocardial Infarction | 2 | (0.0) | 0 | (0.0) |
| Fatal Hemorrhagic Stroke | 1 | (0.0) | 1 | (0.0) |
| Fatal Ischemic Cerebrovascular Stroke | 0 | (0.0) | 1 | (0.0) |
| Sudden Cardiac Death | 3 | (0.1) | 4 | (0.1) |
| Cardiac Events (Fatal/Nonfatal) | 28 | (0.7) | 10 | (0.2) |
| **Acute Myocardial Infarction** | **20** | **(0.5)** | **4** | **(0.1)** |
| Sudden Cardiac Death | 3 | (0.1) | 4 | (0.1) |
| Unstable Angina Pectoris | 5 | (0.1) | 3 | (0.1) |
| **Cerebrovascular Events (Fatal/Nonfatal)†** | **13** | **(0.3)** | **9** | **(0.2)** |
| Hemorrhagic Stroke | 2 | (0.0) | 1 | (0.0) |
| Ischemic Cerebrovascular Stroke | 9 | (0.2) | 8 | (0.2) |
| Transient Ischemic Attack | 2 | (0.0) | 0 | (0.0) |
| **Peripheral Vascular Events (Fatal/Nonfatal)** | **6** | **(0.1)** | **1** | **(0.0)** |
| Peripheral Arterial Thrombosis | 1 | (0.0) | 0 | (0.0) |
| Peripheral Venous Thrombosis | 5 | (0.1) | 1 | (0.0) |
| † Includes hemorrhagic stroke. | | | | |
| Note: Patients may be counted in more than 1 row, but are only counted once within a row. | | | | |

**Deaths:**

There were 37 deaths (all-causes) in this trial: 22 in the Rofecoxib and 15 in the Naproxen groups, respectively. In analyzing causes of death, the Medical Reviewer examined (original submission, 6/29/00) Table 55( Study Report Section 9.3; pdf. Page 169), Patient Narratives (Appendix 4.20.1: beginning pdf. Page 3255), and the Case Report Forms. It should be noted that the death analyses (above tables) in this review were performed with the sponsor's analyses and were not reanalyzed using the data from this Medical Reviewer; it is unclear if the cardiovascular deaths in the sponsor's analyses are the same as those presented below.

In the Rofecoxib group, the following deaths were possible or probable cardiovascular/cerebrovascular events (see Appendix , Table 55 for full table). Items in bold (9 cases) are possibly/probably related to thrombosis/atherosclerosis:

Deaths: Rofecoxib group: Medical Reviewer's analysis

| AN | Study number | Gender | Race | Age | Relative Day of Onset | Adverse experience |
|---|---|---|---|---|---|---|
| 324 | 088022 | M | White | 69 | 174 | **Ventricular fibrillation/Sudden death** |
| 1224 | 088140 | F | White | 68 | 46 | **Myocardial infarction†** |
| 920 | 088148 | F | White | 68 | 205 | **Cerebrovascular accident** |
| 2759 | 088149 | M | White | 69 | 94 | **Myocardial infarction** |

†This patient was classified in Table 55 as "multiple organ failure." However, a review of the patient narrative showed that this patient had a non Q-wave myocardial infarction (with associated symptoms, ECG changes, and cardiac enzyme elevation). The Medical Reviewer, therefore, reclassified this event as myocardial infarction. See sNDA S-007: CSR 088c: pdf page 1286 for further details.

Deaths: Rofecoxib group (cont.)

| AN | Study number | Gender | Race | Age | Relative Day of Onset | Adverse experience |
|---|---|---|---|---|---|---|
| 5305 | 089013 | F | Multi | 75 | 309 | **Cardiac arrest/Sudden death** |
| 7620 | 089021 | F | Multi | 55 | 31 | Dissecting aortic aneurysm |
| 5591 | 089022 | F | White | 51 | 206 | **Cerebrovascular accident** |
| 7973 | 089100 | M | White | 71 | 147 | **Myocardial infarction** |
| 7553 | 089107 | F | Multi | 51 | 28 | **Dyspnea/cyanosis, unknown etiology*** |
| 7689 | 089127 | F | White | 60 | 107 | **Sudden death‡** |

*This patient, coded as "congestive heart failure" in Table 55, presented to the ER with dyspnea and cyanosis, was given aminophylline and subsequently died; the cause of death was registered as "cardiac insufficiency" and no other details (EKG, labs) are given in the narrative. There is no history of asthma in the case report form; screening cardiac/pulmonary exam was normal. See sNDA S-007: CSR 088c: pdf page 1292.
‡This patient was coded in Table 55 as "aortic stenosis." According to the narrative, this patient with hypertension and diabetes died suddenly at home. Autopsy showed cardiac hypertrophy and pulmonary congestion; no finding of aortic valve abnormalities or asymmetric septal hypertrophy were reported. In the case report form, there is notation of "idiopathic hypertrophic subaortic stenosis;" the screening cardiac exam was noted as normal and the patient was on enalapril. No autopsy or echocardiographic findings are reported. Therefore, the Medical Reviewer reclassified this event as sudden death. See sNDA S-007: CSR 088c: pdf page 1293 for further details.

In the Naproxen group, the following five deaths were possible or probable cardiovascular/cerebrovascular events:

Deaths: Naproxen Group: Medical Reviewer's Analysis

| AN | Study number | Gender | Race | Age | Relative Day of Onset | Adverse experience |
|---|---|---|---|---|---|---|
| 2923 | 088003 | M | White | 60 | 164 | **Cerebrovascular accident** |
| 2632 | 088163 | F | White | 70 | 17 | **Sudden death*** |
| 7732 | 089016 | M | White | 62 | 61 | **Sudden death ** ** |
| 2229 | 088175 | F | White | 79 | 247 | Intracranial hemorrhage |
| 6703 | 089076 | F | White | 53 | 205 | Intracranial hemorrhage |
| 7769 | 089021 | M | White | 58 | 266 | **Myocardial infarction/Sudden death°** |
| 6057 | 089054 | M | White | 70 | 200 | **Myocardial infarction/Sudden death°** |

The Reviewer has marked in bold those events possibly related to thrombosis/ischemia.
*Coded in Table 55 as myocardial infarction; however, this was sudden death according to the narrative.
** Coded in Table 55 as Unknown cause of death; according to the narrative, this patient was found dead in his home. The only additional information is a complaint of cough and chest pain the day before his demise.
°Coded as myocardial infarction; however, there is no documentation for myocardial infarction in the case report form. These patients were not hospitalized and are listed as deaths.

**Subgroup analyses of cardiovascular serious adverse experiences:**

The sponsor has provided a subgroup analysis in the 10/13/00 safety update. The relative risk estimate is not significant only in the hypertensive subgroup.

Summary of Adjudicated Thromboembolic Serious AEs in Selected Subgroups
of Patients With Rheumatoid Arthritis in VIGOR
Safety Update Report

| Subgroup | Treatment | N | Patients With Events | PYR[†] | Rates[‡] | Relative Risk[§] Estimate | 95% CI |
|---|---|---|---|---|---|---|---|
| Males | Rofecoxib | 824 | 20 | 548 | 3.65 | | |
| | Naproxen | 814 | 7 | 556 | 1.26 | 0.34 | (0.15, 0.81) |
| Females | Rofecoxib | 3223 | 25 | 2149 | 1.16 | | |
| | Naproxen | 3215 | 12 | 2142 | 0.56 | 0.48 | (0.24, 0.96) |
| 65+ years old | Rofecoxib | 997 | 28 | 621 | 4.51 | | |
| | Naproxen | 1070 | 13 | 662 | 1.97 | 0.43 | (0.22, 0.84) |
| <65 years old | Rofecoxib | 3050 | 17 | 2076 | 0.82 | | |
| | Naproxen | 2959 | 6 | 2037 | 0.29 | 0.36 | (0.14, 0.91) |
| Current smoker | Rofecoxib | 790 | 17 | 516 | 3.29 | | |
| | Naproxen | 779 | 5 | 533 | 0.94 | 0.28 | (0.10, 0.76) |
| Ex/never smoker | Rofecoxib | 3256 | 28 | 2180 | 1.28 | | |
| | Naproxen | 3250 | 14 | 2165 | 0.65 | 0.50 | (0.26, 0.96) |
| Cardiovascular history | Rofecoxib | 238 | 16 | 147 | 10.92 | | |
| | Naproxen | 216 | 5 | 139 | 3.60 | 0.33 | (0.12, 0.90) |
| No cardiovascular history | Rofecoxib | 3809 | 29 | 2550 | 1.14 | | |
| | Naproxen | 3813 | 14 | 2559 | 0.55 | 0.48 | (0.25, 0.91) |
| Hypertensive | Rofecoxib | 1217 | 20 | 790 | 2.53 | | |
| | Naproxen | 1168 | 12 | 762 | 1.58 | 0.62 | (0.30, 1.27) |

Aspirin indicated /Aspirin not indicated subgroup:
The sponsor has provided an analysis based on the subgroup of patients meeting criteria for aspirin use for cardioprotection (i.e. those who might have benefitted from low-dose aspirin use). It can be seen that there are higher rates of events in the rofecoxib group (with significant confidence intervals) in both subgroups.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Incidence of Adjudicated Thrombotic Cardiovascular Serious Adverse Experiences in Patient Subgroups | | | | | | | | |
| | Based on a Past Medical History Meeting Criteria for Vascular-Protective Aspirin Therapy | | | | | | | | |
| | VIGOR Study in Rheumatoid Arthritis Patients | | | | | | | | |
| | Updated Application Data | | | | | | | | |
| | | | | | | | | | |
| | | Treatment | | Patients With | | | Relative Risk[§] | | |
| | Subgroup | Group | N | Events | PYR[†] | Rates[‡] | Estimate | 95% CI | |
| | | | | | | | | | |
| All patients | | Rofecoxib | 4047 | 45 | 2697 | 1.67 | | | |
| | | Naproxen | 4029 | 19 | 2698 | 0.70 | 0.42 | (0.25, 0.72) | |
| Aspirin indicated[%], ¶ | | Rofecoxib | 170 | 15 | 105 | 14.29 | | | |
| | | Naproxen | 151 | 3 | 102 | 2.94 | 0.20 | (0.06, 0.71) | |
| | | | | | | | | | |
| Aspirin not indicated[%] | | Rofecoxib | 3877 | 30 | 2592 | 1.16 | | | |
| | | Naproxen | 3878 | 16 | 2596 | 0.62 | 0.53 | (0.29, 0.97) | |
| † | Patient-years at risk. | | | | | | | | |
| ‡ | Per 100 PYR. | | | | | | | | |
| § | Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates. | | | | | | | | |
| % | The "Aspirin Indicated" cohort represents those patients with a past medical history of cerebrovascular accident, transient ischemic attack, | | | | | | | | |
| | myocardial infarction, unstable angina, stable angina, coronary artery bypass graft surgery, or percutaneous coronary intervention [3]. | | | | | | | | |
| | "Aspirin Not Indicated" cohort represents those patients who did not have a past medical history of any of these diseases. | | | | | | | | |
| ¶ | Treatment-by-aspirin indicated subgroup interaction test, p=0.177. | | | | | | | | |

(Source: Safety Update: Table 9: pdf. Page 21. 10/13/00)

To assess the role of edema and hypertension in those patients with confirmed thrombotic events, the sponsor performed the following analyses:

Only 1 patient in each treatment group had both a confirmed thrombotic cardiovascular experience and edema. It appears that there is no relationship between the incidence of edema and confirmed thrombotic cardiovascular experiences.

| Incidence of Edema-Related Adverse Experiences in Patients With and Without Confirmed Thrombotic Cardiovascular Serious Adverse Experiences<br>VIGOR Study in Rheumatoid Arthritis Patients<br>Updated Application Data | | | | |
|---|---|---|---|---|
| | | | Patients With an Edema-Related Adverse Experience | |
| Subgroup | Treatment Group | N | n | (%) |
| Incidence of an Edema-Related Adverse Experience | | | | |
| Patients with a confirmed thrombotic cardiovascular serious adverse experience | Rofecoxib | 45 | 1 | (2.2) |
| Patients without a confirmed thrombotic cardiovascular serious adverse experience | Rofecoxib | 4002 | 219 | (5.5) |
| Patients with a confirmed thrombotic cardiovascular serious adverse experience | Naproxen | 19 | 1 | (5.3) |
| Patients without a confirmed thrombotic cardiovascular serious adverse experience | Naproxen | 4010 | 144 | (3.6) |
| Data Source: [P088C], [Attachment 3] | | | | |

(Source: 10/13/00 Safety Update: Table 17: pdf. Page 27)

| Incidence of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in Patients With and Without Edema-Related Adverse Experiences<br>VIGOR Study in Rheumatoid Arthritis Patients<br>Updated Application Data | | | | |
|---|---|---|---|---|
| | | | Patients With a Confirmed Cardiovascular Serious Adverse Experience | |
| Subgroup | Treatment Group | N | n | (%) |
| Incidence of Confirmed Thrombotic Cardiovascular Serious Adverse Experience | | | | |
| Patients with an edema-related adverse experience | Rofecoxib | 220 | 1 | (0.5) |
| Patients without an edema-related adverse experience | Rofecoxib | 3827 | 44 | (1.1) |
| Patients with an edema-related adverse experience | Naproxen | 145 | 1 | (0.7) |
| Patients without an edema-related adverse experience | Naproxen | 3884 | 18 | (0.5) |
| Data Source: [P088C], [Attachment 3] | | | | |

(Source:10/13/00 Safety Update: Table 15: pdf. Page 26)

A similar analysis was done for hypertension and confirmed thrombotic cardiovascular experiences. Of the patients with confirmed events, a higher percent in the rofecoxib group also developed a hypertension-related adverse experience; however, most of the patients with a hypertension-related adverse experience did not have a confirmed cardiovascular thrombotic event.

| Incidence of Hypertension-Related Adverse Experiences in Patients With and Without Confirmed Thrombotic Cardiovascular Serious Adverse Experiences<br>VIGOR Study in Rheumatoid Arthritis Patients<br>Updated Application Data | | | | |
|---|---|---|---|---|
| Subgroup | Treatment Group | N | Patients With a Hypertension-Related Adverse Experience n | (%) |
| Incidence of a Hypertension-Related Adverse Experience | | | | |
| Patients with a confirmed thrombotic cardiovascular serious adverse experience | Rofecoxib | 45 | 7 | (15.6) |
| Patients without a confirmed thrombotic cardiovascular serious adverse experience | Rofecoxib | 4002 | 387 | (9.7) |
| Patients with a confirmed thrombotic cardiovascular serious adverse experience | Naproxen | 19 | 1 | (5.3) |
| Patients without a confirmed thrombotic cardiovascular serious adverse experience | Naproxen | 4010 | 220 | (5.5) |

(Source: 10/13/00 Safety Update: Table 13: pdf. page 25)

| Incidence of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in Patients With and Without Hypertension-Related Adverse Experiences<br>VIGOR Study in Rheumatoid Arthritis Patients<br>Updated Application Data | | | | |
|---|---|---|---|---|
| Subgroup | Treatment Group | N | Patients With a Confirmed Cardiovascular Serious Adverse Experience n | (%) |
| Incidence of a Confirmed Thrombotic Cardiovascular Serious Adverse Experience | | | | |
| Patients with a hypertension-related adverse experience | Rofecoxib | 394 | 7 | (1.8) |
| Patients without a hypertension-related adverse experience | Rofecoxib | 3653 | 38 | (1.0) |
| Patients with a hypertension-related adverse experience | Naproxen | 221 | 1 | (0.5) |
| Patients without a hypertension-related adverse experience | Naproxen | 3808 | 18 | (0.5) |

(Source: 10/13/00 Safety Update: Table 11: pdf. Page 24)

**Comments:**

This is a large comparative study using rofecoxib 50 mg daily and naproxen 1000 mg daily in patients with rheumatoid arthritis. A significant difference is seen in the composite of stroke, myocardial infarction, and cardiac death which is unfavorable for rofecoxib; consistent with this result are the time-to-event tables, and myocardial infarction, and ( by the reviewer's analysis) cardiovascular death events.

***Study 085:***

Title: A Randomized, Placebo-Controlled, Parallel Group, Double Blind Study to Evaluate the Efficacy and Safety of MK-0966 12.5 mg vs. Nabumetone 1000 mg in Patients with Osteoarthritis of the Knee.

Primary Objective: To demonstrate superiority of MK-0966 12.5 mg to nabumetone 1000 mg in the percent of patients with good or excellent response to therapy as assessed by Patient Global Assessment of Response to Therapy in the treatment of osteoarthritis of the knee during a 6 week treatment period.

Secondary Objectives: There were 5 secondary objectives, related to efficacy of each drug versus placebo and superiority claims of rofecoxib over nabumetone using various instruments (Patient and/or Investigator Assessments of Response to Therapy) over 6 weeks.

Study design: This was a randomized, double-blind, parallel-group , placebo-controlled study of efficacy and safety or rofecoxib versus nabumetone after 6 weeks of treatment for osteoarthritis of the knee. Eligible patients were males or females over 40 years old with osteoarthritis of the knee for at least 6 months.

The rationale for dose selection was that in another study (Protocol 010), both 25 mg and 125 mg of rofecoxib were efficacious and indistinguishable in the treatment of osteoarthritis in a 6 week study; it was felt by the sponsor that there was a plateau for rofecoxib in the range of 12.5 to 25 mg. The starting dose of nabumetone (1000 mg) was chosen as the comparator. A placebo arm was included in this study with acetaminophen as the rescue medication.

**Of note, patients in this study were allowed to take low-dose aspirin for cardioprotection.** Full-dose aspirin or NSAIDs were not allowed during the treatment period. However, patients were not randomized to low-dose aspirin versus non-aspirin use.

Safety measurements included spontaneously reported adverse events, percent of patients that discontinue prematurely due to drug related adverse events, physical examination, vital signs, body weight and laboratory data.

**Results:**

1495 patients were screened at 113 study sites; of these, 1042 patients were randomized in a 2:2:1 ratio to rofecoxib 12.5 mg (N=424), nabumetone 1000 mg (N= 410) or placebo (N=208).

The 3 treatment groups were similar in regard to baseline characteristics. The mean age was 63.1 years (range 35-92 years); this was a majority (68.3%) female, mostly (87.9%) white population. Of the concurrent conditions, 42.1% had hypertension, , 16.9% had hypercholesterolemia, 8.3% had hyperlipidemia, and 12.4% were obese; most patients (91.0%) reported no current tobacco use and 89.1% consumed $\leq$ 4 drinks/week alcohol consumption. Throughout the trial, 11.9% of patients took low-dose aspirin (81 mg or less, once daily) for cardioprotection.
Rates of noncompliance were slightly higher in the placebo group (10.1%) but were similar between rofecoxib and nabumetone (both were 6.6%, respectively).

Of 1042 randomized, 816 (78.3%) completed the study; the percentage of those completing the study was significantly higher in the rofecoxib (82.5%) and nabumetone (79.3%) arms than placebo (67.8%, $p \leq .002$). The most frequent reason for discontinuation was lack of efficacy, which was highest in the placebo group (23%, $p < .001$ compared to rofecoxib or nabumetone). The second most frequent reason for discontinuation was clinical adverse experience, which was higher than placebo but not significantly different between treatment groups.

| | | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | MK-0966 12.5 mg | | Nabumetone 1000 mg | | Placebo | | Patients | |
| | N=(424) | | N=(410) | | N=(208) | | N=(1042) | |
| | n | (%) | n | (%) | n | (%) | n (%) | |
| NUMBER OF PATIENTS SCREENED | | | | | | | 1495 | |
| NUMBER OF PATIENTS NOT RANDOMIZED | | | | | | | 453 | |
| NUMBER OF PATIENTS RANDOMIZED | 424 | | 410 | | 208 | | 1042 | |
| COMPLETED STUDY | 350 | ( 82.5) | 325 | ( 79.3) | 141 | ( 67.8) | 816 | ( 78.3) |
| DISCONTINUED STUDY | 74 | ( 17.5) | 85 | ( 20.7) | 67 | ( 32.2) | 226 | ( 21.7) |
| CLINICAL AE | 24 | ( 5.7) | 25 | ( 6.1) | 6 | ( 2.9) | 55 | ( 5.3) |
| LABORATORY AE | 0 | ( 0.0) | 1 | ( 0.2) | 1 | ( 0.5) | 2 | ( 0.2) |
| DEVIATION FROM PROTOCOL | 4 | ( 0.9) | 4 | ( 1.0) | 6 | ( 2.9) | 14 | ( 1.3) |
| PATIENT LOST TO FOLLOW-UP | 5 | ( 1.2) | 1 | ( 0.2) | 0 | ( 0.0) | 6 | ( 0.6) |
| PATIENT WITHDREW CONSENT | 8 | ( 1.9) | 4 | ( 1.0) | 5 | ( 2.4) | 17 | ( 1.6) |
| PATIENT WAS DISCONTINUED DUE | | | | | | | | |
| TO LACK OF TEST DRUG EFFICACY | 31 | ( 7.3) | 47 | ( 11.5) | 49 | ( 23.6) | 127 | ( 12.2) |
| OTHER | 2 | ( 0.5) | 3 | ( 0.7) | 0 | ( 0.0) | 5 | ( 0.5) |

Adapted from: 085 : pdf. page 817

**Safety:**

There were no deaths in this study.

The following table is taken from the sponsor). About half of the patients in each treatment arm had at least one adverse experience.

Of the clinical adverse experiences reported (≥ 1%) by Body System, none are reported as cardiovascular adverse experiences. Of the serious adverse experiences, 3 are cardiovascular (1 in rofecoxib, 2 in nabumetone, 0 in placebo) in nature.

Clinical Adverse Experience Summary

| | Rofecoxib 12.5 mg (N=424) n (%) | Nabumetone 1000 mg (N=410) n (%) | Placebo (N=208) n (%) |
|---|---|---|---|
| Number (%) of patients: | | | |
| with one or more adverse experiences | 212 (50.0) | 197 (48.0) | 104 (50.0) |
| with no adverse experience | 212 (50.0) | 213 (52.0) | 104 (50.0) |
| with serious adverse experiences | 4 (0.9) | 8 (2.0) | 1 (0.5) |
| who died | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| discontinued due to an adverse experience | 24 (5.7) | 24 (5.9)‡ | 8 (3.8)§ |
| discontinued due to a serious adverse experience | 2 (0.5) | 3 (0.7) | 0 (0.0) |

‡ AN 1446 in the nabumetone group was counted as discontinuing due to a clinical adverse experience of diverticulosis which began prior to randomization.

§ AN 0052 in the placebo group was counted as discontinuing due to phimosis and balanitis, even though he was counted in the Patient Status Summary as discontinuing due to a protocol violation. AN 0664 in the placebo group was counted as discontinuing due to unbearable osteoarthritis pain, even though he was counted in the Patient Status Summary as discontinuing due to lack of test drug efficacy.

Note: This table presents counts of patients. Patients are counted only once per category but may be counted in more than 1 category.

Data Source: [4.1.41; 4.12]

(sNDA: 085 clinical study report: Table 34, pdf. page 102)

Of the serious cardiovascular clinical adverse experiences, 2 can be found in the rofecoxib group and 2 in the nabumetone group, respectively. No serious cardiovascular clinical adverse experiences are noted in the placebo group.

Rofecoxib

| AN | Study number | Gender | Race | Age | Adverse Experience | Rel. Day of Onset | Action Taken with Drug | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1067 | 021 | M | White | 70 | Cardiac trauma | 12 | None | Recovered |
| 1353 | 072 | F | White | 75 | Myocardial infarction | 40 | Discontinued | Recovered |

Nabumetone

| An | Study number | Gender | Race | Age | Adverse Experience | Rel. Day of Onset | Action Taken with Drug | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1273 | 081 | F | White | 77 | Urinary tract infection | 3 | None | Recovered |
| | | | | | **Congestive heart failure** | **4** | **None** | **Recovered** |
| **1211** | **082** | **F** | **White** | **67** | **Coronary artery disease** | **18** | **Discontinued** | **Not recovered** |

(Source: 085: Table38: pdf. Page 109.)

The following table lists adverse experiences related to edema, fluid retention, hypertension, and congestive heart failure. More edema is seen in the rofecoxib group; no significant differences are seen in regard to hypertension.

Summary of Renal/Vascular Effects†

| | Treatment Group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Rofecoxib 12.5 mg (N=424) | | Nabumetone 1000 mg (N=410) | | Placebo (N=208) | | Total (N=1042) | |
| | n | (%) | n | (%) | n | (%) | n | (%) |
| **Specific Edema-Related Adverse Experiences** | **15** | **(3.5)** | **8** | **(2.0)** | **3** | **(1.4)** | **26** | **(2.5)** |
| Edema | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 1 | (0.1) |
| Facial edema | 0 | (0.0) | 1 | (0.2) | 0 | (0.0) | 1 | (0.1) |
| Lower extremity edema | 10 | (2.4) | 7 | (1.7) | 2 | (1.0) | 19 | (1.8) |
| Peripheral edema | 0 | (0.0) | 1 | (0.2) | 0 | (0.0) | 1 | (0.1) |
| Upper extremity edema | 3 | (0.7) | 2 | (0.5) | 1 | (0.5) | 6 | (0.6) |
| Fluid retention | 1 | (0.2) | 0 | (0.0) | 0 | (0.0) | 1 | (0.1) |
| **Other Adverse Experiences Possibly Related to Fluid Retention** | **0** | **(0.0)** | **2** | **(0.5)** | **0** | **(0.0)** | **2** | **(0.2)** |
| Congestive heart failure | 0 | (0.0) | 2 | (0.5) | 0 | (0.0) | 2 | (0.2) |
| **Hypertension/Increased Blood Pressure** | **5** | **(1.2)** | **7** | **(1.7)** | **3** | **(1.4)** | **15** | **(1.4)** |
| Blood pressure increased | 2 | (0.5) | 2 | (0.5) | 0 | (0.0) | 4 | (0.4) |
| Hypertension | 3 | (0.7) | 4 | (1.0) | 2 | (1.0) | 9 | (0.9) |
| Systolic hypertension | 0 | (0.0) | 0 | (0.0) | 1 | (0.5) | 1 | (0.1) |
| Uncontrolled hypertension | 0 | (0.0) | 1 | (0.2) | 0 | (0.0) | 1 | (0.1) |

† Based on edema-related and hypertensive adverse experiences.

Note: This table presents counts of patients. Patients are counted only once per category (in bold-faced type) but may be counted in more than 1 category.

(Source: 085: pdf. page 117)

Another subgroup analysis (below) was done by aspirin user vs. non-aspirin user. It can be noted that most of the patients who had a serious adverse experience or who discontinued due to an adverse experience were in the non-aspirin user subgroup. However, the usefulness of this analysis is limited by the differences in sample size (low-dose aspirin user versus non-aspirin user) and by the fact that these groups were not randomized; i.e., results due to differences in baseline patient characteristics cannot be excluded.

Clinical Adverse Experience Summary by Aspirin Subgroup

| | Rofecoxib 12.5 mg (N=424) | | | | Nabumetone 1000 mg (N=410) | | | | Placebo (N=208) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Low-Dose Aspirin (N=46) | | Non-User (N=378) | | Low-Dose Aspirin (N=57) | | Non-User (N=353) | | Low-Dose Aspirin (N=21) | | Non-User (N=187) | |
| | n | % | n | % | n | % | n | % | n | % | n | % |
| Number (%) of patients: | | | | | | | | | | | | |
| With one or more adverse experiences | 23 | (50.0) | 189 | (50.0) | 22 | (38.6) | 175 | (49.6) | 8 | (38.1) | 96 | (51.3) |
| With no adverse experience experiences | 23 | (50.0) | 189 | (50.0) | 35 | (61.4) | 178 | (50.4) | 13 | (61.9) | 91 | (48.7) |
| With serious adverse experiences | 0 | (0.0) | 4 | (1.1) | 3 | (5.3) | 5 | (1.4) | 0 | (0.0) | 1 | (0.5) |
| Who died | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to an adverse experience | 3 | (6.5) | 21 | (5.6) | 2 | (3.5) | 22 | (6.2) | 0 | (0.0) | 8 | (4.3) |
| Discontinued due to a serious adverse experience | 0 | (0.0) | 2 | (0.5) | 0 | (0.0) | 3 | (0.8) | 0 | (0.0) | 0 | (0.0) |

Data Source: [4.1.58; 4.1.59]

**Comments:**

Because of the smaller sample size and event rates, the results of this study do not convince this reviewer that there is no safety issue with rofecoxib. Furthermore, the dose of rofecoxib, 12.5 mg, is lower than that used in the rofecoxib treatment arm in the VIGOR study. An increase in cardiovascular events at higher doses of rofecoxib cannot be excluded.

***Study 090:***

**Title:** A randomized, placebo-controlled, parallel-group, double-blind study to evaluate the efficacy and safety of MK-0966 (Rofecoxib) 12.5 mg versus Nabumetone 1000 mg in patients with osteoarthritis of the knee

Primary Objective: To demonstrate superiority of rofecoxib 12.5 mg to nabumetone 1000 mg
in the percent of patients with good or excellent response to therapy, as
assessed by PGART (Patient Global Assessment of Response to Therapy), in the treatment of osteoarthritis of the knee during a 6-week treatment period.

Secondary Objectives:
As with study 085, the secondary objectives were superiority of rofecoxib to nabumetone and efficacy of both drugs to placebo, using assessment instruments of response to therapy.
in the percent of patients with good or excellent response to therapy, as
Study design:
This was a double-blind, parallel-group, placebo-controlled study comparing efficacy and safety of rofecoxib versus nabumetone after 6 weeks of treatment for osteoarthritis of the knee. Following a screening period, eligible patients were randomized to either rofecoxib 12.5 mg daily, nabumetone 1000 mg daily, or placebo for 6 weeks.

Safety measurements were to include recording of adverse experiences, vital signs, and collection of laboratory data at Weeks 2 and 6.

**Of note, low-dose aspirin (81 mg or less per day) for cardioprotection was allowed in this study.** Concomitant use of NSAIDS and high-dose aspirin, however, were prohibited during the treatment period.

Prespecified in this study was a subgroup analysis of safety for aspirin users and non-aspirin users.

Results:

A total of 1457 patients were screened for enrollment at 115 study sites. Of these, 978 patients with osteoarthritis of the knee were randomized in a 2:2:1 ratio to 1 of 3 treatment groups: rofecoxib 12.5 mg (N=390), nabumetone 1000 mg (N=392), or placebo (N=196).

| | Patient Accounting | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Rofecoxib | | Nabumetone | | | | | |
| | 12.5 mg | | 1000 mg | | Placebo | | Total | |
| ENTERED: | 390 | | 392 | | 196 | | 978 | |
| Male (age range) | 119 (40 to 87) | | 114 (40 to 86) | | 60 (41 to 81) | | 293 (40 to 87) | |
| Female (age range) | 271 (37 to 85) | | 278 (37 to 90) | | 136 (41 to 83) | | 685 (37 to 90) | |
| | n (%) | | n (%) | | n (%) | | n (%) | |
| COMPLETED: | 322 | (82.6)* | 324 | (82.7)* | 143 | (73.0) | 789 | (80.7) |
| DISCONTINUED: | 68 | (17.4) | 68 | (17.3) | 53 | (27.0) | 189 | (19.3) |
| Clinical adverse experience | 29 | (7.4)*,** | 15 | (3.8)† | 7 | (3.6)‡ | 51 | (5.2) |
| Laboratory adverse experience | 2 | (0.5) | 0 | (0.0) | 0 | (0.0) | 2 | (0.2) |
| Deviation from protocol | 5 | (1.3) | 6 | (1.5) | 3 | (1.5) | 14 | (1.4) |
| Patient lost to follow-up | 2 | (0.5) | 3 | (0.8) | 4 | (2.0) | 9 | (0.9) |
| Patient withdrew consent | 2 | (0.5) | 4 | (1.0) | 2 | (1.0) | 8 | (0.8) |
| Lack of efficacy | 27 | (6.9)* | 39 | (9.9)* | 37 | (18.9) | 103 | (10.5) |
| Other | 1 | (0.3) | 1 | (0.3) | 0 | (0.0) | 2 | (0.2) |
| † AN 2674 and AN 2676 in the nabumetone group were counted as discontinuing due to lack of test drug efficacy, even | | | | | | | | |
| though they had an adverse experience of increased osteoarthritis pain which was considered to cause discontinuation. | | | | | | | | |
| ‡ AN 3313 in the placebo group was counted as discontinuing due to a clinical adverse experience of neck pain, which began prior to randomization. | | | | | | | | |
| AN 2778 in the placebo group was counted as discontinuing due to a clinical adverse experience of worsening headaches, which began prior to randomization. | | | | | | | | |
| * p .0.05 versus placebo. | | | | | | | | |
| ** p .0.05 versus nabumetone. | | | | | | | | |

(Source: 090: Table 15: pdf. page 64)

The 3 treatment groups were very similar with regard to demographic characteristics. Patients ranged in age from 37 to 90 years, with a mean age of 62.7 years. Although the lower age limit for inclusion in this study was 40 years, two 37-year-old patients were inadvertently enrolled in the study (one each from rofecoxib and nabumetone). Both patients met all other selection criteria and were included in all efficacy and safety analyses. The majority (70.0%) of patients were female, and most patients (87.6%) were white.

Baseline Patient Demographic Characteristics by Treatment Group

| | Rofecoxib 12.5 mg (N=390) | | Nabumetone 1000 mg (N=392) | | Placebo (N=196) | | Total (N=978) | |
|---|---|---|---|---|---|---|---|---|
| **Gender (n, %)** | | | | | | | | |
| Female | 271 | (69.5) | 278 | (70.9) | 136 | (69.4) | 685 | (70.0) |
| Male | 119 | (30.5) | 114 | (29.1) | 60 | (30.6) | 293 | (30.0) |
| **Age (n, %)** | | | | | | | | |
| 40 years | 3 | (0.8) | 3 | (0.8) | 0 | (0.0) | 6 | (0.6) |
| 41 to 65 years | 232 | (59.5) | 215 | (54.8) | 115 | (58.7) | 562 | (57.5) |
| 66 years | 155 | (39.7) | 174 | (44.4) | 81 | (41.3) | 410 | (41.9) |
| Mean (SD) | 62.3 (10.2) | | 63.2 (10.7) | | 62.3 (10.1) | | 62.7 (10.4) | |
| Range | 37 to 87 | | 37 to 90 | | 41 to 83 | | 37 to 90 | |
| **Race (n, %)** | | | | | | | | |
| Asian | 4 | (1.0) | 4 | (1.0) | 0 | (0.0) | 8 | (0.8) |
| Black | 26 | (6.7) | 33 | (8.4) | 14 | (7.1) | 73 | (7.5) |
| Hispanic | 15 | (3.8) | 12 | (3.1) | 7 | (3.6) | 34 | (3.5) |
| Indian (India) | 0 | (0.0) | 0 | (0.0) | 1 | (0.5) | 1 | (0.1) |
| Native American | 2 | (0.5) | 2 | (0.5) | 0 | (0.0) | 4 | (0.4) |
| White | 342 | (87.7) | 341 | (87.0) | 174 | (88.8) | 857 | (87.6) |
| Native American and White | 1 | (0.3) | 0 | (0.0) | 0 | (0.0) | 1 | (0.1) |

Data Source: [4.1.3; 4.2]
(Source: 090: pdf. Page 56)

The 3 treatment groups were also similar with regard to baseline arthritis, body mass index, arthritis treatment history; of baseline secondary diagnoses: 41.1% had hypertension, 17.6% had hypercholesterolemia, and 8.7% had obesity. There appeared to be no clinically meaningful differences between the 3 treatment groups. Low-dose aspirin for cardioprotection was used by 12.2% of patients in this study; no meaningful differences were noted in percent of aspirin use among the 3 treatment groups.

Safety:

There were no deaths in this study. The next page shows a summary of total adverse experiences.

Clinical Adverse Experience Summary

| Number (%) of patients: | Rofecoxib 12.5 mg (N=390) n | (%) | Nabumetone 1000 mg (N=392) n | (%) | Placebo (N=196) n | (%) | Total (N=978) n | (%) |
|---|---|---|---|---|---|---|---|---|
| With one or more adverse experiences | 220 | (56.4)*,** | 193 | (49.2) | 84 | (42.9) | 497 | (50.8) |
| With no adverse experience | 170 | (43.6) | 199 | (50.8) | 112 | (57.1) | 481 | (49.2) |
| With serious adverse experiences | 9 | (2.3)** | 2 | (0.5) | 1 | (0.5) | 12 | (1.2) |
| Who died | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to an adverse experience | 29 | (7.4)* | 17 | (4.3)‡ | 5 | (2.6)§ | 51 | (5.2) |
| Discontinued due to a serious adverse experience | 8 | (2.1)** | 1 | (0.3) | 1 | (0.5) | 10 | (1.0) |

‡ AN 2674 and AN 2676 in the nabumetone group were counted as discontinuing due to increased osteoarthritis pain, even though they were counted in the Patient Status Summary as discontinuing due to lack of test drug efficacy.

§ AN 3313 in the placebo group was counted as discontinuing due to a clinical adverse experience of neck pain which began prior to randomization. AN 2778 in the placebo group was counted as discontinuing due to a clinical adverse experience of worsening headaches, which began prior to randomization.

* p 0.05 versus placebo.

** p 0.05 versus nabumetone.

Note: This table presents counts of patients. Patients are counted only once per category but may be counted in more than 1 category

Data Source: [4.1.4; 4.12]

(Source: 090: pdf. Page 107)

Number (%) of Patients With Clinical Adverse Experiences
(Incidence 1% in One or More Treatment Groups by Body System

| | Rofecoxib 12.5 mg (N=390) n | (%) | Nabumetone 1000 mg (N=392) n | (%) | Placebo (N=196) n | (%) | Total (N=978) n | (%) |
|---|---|---|---|---|---|---|---|---|
| Patients with one or more clinical adverse experiences | 220 | (56.4) | 193 | (49.2) | 84 | (42.9) | 497 | (50.8) |
| Patients with no clinical adverse experience | 170 | (43.6) | 199 | (50.8) | 112 | (57.1) | 481 | (49.2) |
| **Body as a Whole/Site** | 73 | (18.7) | 75 | (19.1) | 36 | (18.4) | 184 | (18.8) |
| **Cardiovascular System** | **17** | **(4.4)** | **8** | **(2.0)** | **6** | **(3.1)** | **31** | **(3.2)** |
| Hypertension | 6 | (1.5) | 2 | (0.5) | 2 | (1.0) | 10 | (1.0) |

Adapted from: 090: Table 35: pdf. page 110.

Below is a listing of serious cardiovascular adverse experiences (AE). In the rofecoxib group, a total of 6 serious cardiovascular AE were reported; in the nabumetone group, there were 2 AE, and in the placebo group, 1 AE, respectively. There were more myocardial infarctions in the rofecoxib group; however, the event rates are low.

Listing of Patients With Serious Clinical Adverse Experiences

| AN | Study Number | Gender | Race | Age | Adverse Experience | Relative Day of Onset | Action Taken With Drug | Outcome |
|---|---|---|---|---|---|---|---|---|
| **Rofecoxib** | | | | | | | | |
| 2695 | 015 | F | White | 63 | Myocardial infarction | 8 | Discontinued | Recovered |
| 2224 | 022 | M | White | 58 | Cerebrovascular accident | 27 | Discontinued | Recovered |
| 2683 | 049 | M | White | 77 | Atrial fibrillation | 32 | Discontinued | Recovered |
| 2256 | 069 | M | White | 77 | Myocardial infarction | 15 | Discontinued | Recovered |
| 3177 | 079 | F | White | 75 | Cerebrovascular accident | 21 | Discontinued | Recovered |
| 3286 | 103 | F | White | 67 | Myocardial infarction | 1 | Discontinued | Recovered |
| **Nabumetone** | | | | | | | | |
| 3441 | 014 | F | White | 71 | Congestive heart failure | 26 | Interrupted | Recovered |
| 3012 | 112 | F | White | 72 | Myocardial infarction | 3 | Discontinued | Recovered |
| **Placebo** | | | | | | | | |
| 2502 | 087 | M | White | 48 | Coronary artery occlusion | 22 | Discontinued | Recovered |

(Source: 090: Table 38: pdf. Page 116)

More patients in the rofecoxib group discontinued due to cardiovascular adverse experiences than in the nabumetone or placebo groups. (Of the 7 in the rofecoxib group, 3 were listed as having a myocardial infarction, 2 as stroke, 1 as atrial fibrillation, and 1 with hypertension, respectively).

Number (%) of Patients Who Discontinued Due to Clinical Adverse Experiences
(Incidence >0% in One or More Treatment Groups)
by Body System

| | Rofecoxib 12.5 mg (N=390) | | Nabumetone 1000 mg (N=392) | | Placebo (N=196) | | Total (N=978) | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Patients with one or more clinical adverse experiences | 29 | (7.4) | 17 | (4.3) | 5 | (2.6) | 51 | (5.2) |
| Patients with no clinical adverse experience | 361 | (92.6) | 375 | (95.7) | 191 | (97.4) | 927 | (94.8) |
| **Cardiovascular System** | **7** | **(1.8)** | **1** | **(0.3)** | **1** | **(0.5)** | **9** | **(0.9)** |

Adapted from: 090: Table 39: pdf. page 120

APPEARS THIS WAY
ON ORIGINAL

Summary of Renal/Vascular Adverse Experiences†

| Category | Treatment Group: Rofecoxib 12.5 mg (N=390) n | (%) | Nabumetone 1000 mg (N=392) n | (%) | Placebo (N=196) n | (%) | Total (N=978) n | (%) |
|---|---|---|---|---|---|---|---|---|
| **Specific Edema-Related Adverse Experiences** | **12** | **(3.1)** | **10** | **(2.6)** | **4** | **(2.0)** | **26** | **(2.7)** |
| Edema | 1 | (0.3) | 2 | (0.5) | 1 | (0.5) | 4 | (0.4) |
| Lower extremity edema | 10 | (2.6) | 7 | (1.8) | 1 | (0.5) | 18 | (1.8) |
| Upper extremity edema | 1 | (0.3) | 1 | (0.3) | 0 | (0.0) | 2 | (0.2) |
| Fluid retention | 1 | (0.3) | 0 | (0.0) | 2 | (1.0) | 3 | (0.3) |
| **Fluid Retention** | | | | | | | | |
| Congestive heart failure | 0 | (0.0) | 1 | (0.3) | 0 | (0.0) | 1 | (0.1) |
| **Hypertension/Increased Blood Pressure** | **7** | **(1.8)** | **3** | **(0.8)** | **3** | **(1.5)** | **13** | **(1.3)** |
| Blood pressure increased | 1 | (0.3) | 1 | (0.3) | 0 | (0.0) | 2 | (0.2) |
| Hypertension | 6 | (1.5) | 2 | (0.5) | 2 | (1.0) | 10 | (1.0) |
| Hypertensive crisis | 0 | (0.0) | 0 | (0.0) | 1 | (0.5) | 1 | (0.1) |

† Based on edema-related and hypertensive adverse experiences.
Note: This table presents counts of patients. Patients are counted only once per category (in bold-faced type) but may be
counted in more than 1 category.
Data Source: [4.1.56; 4.12.3]
Adapted from 090: Table 43: page 130

The following table represents an analysis of adverse events by aspirin use.

| | Clinical Adverse Experience Summary by Aspirin Subgroup: Rofecoxib 12.5 mg (N=390) | | | | Nabumetone 1000 mg (N=392) | | | | Placebo (N=196) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Clinical Adverse Experiences** | Low dose aspirin (N=45) | | Non-user (N=345) | | Low dose aspirin (N=47) | | Non-user (N=345) | | Low dose aspirin (N=27) | | Non-user (N=169) | |
| Number (%) of Patients | n | % | n | % | n | % | n | % | n | % | n | % |
| With one or more adverse experiences | 30 | (66.7) | 190 | (55.1) | 30 | (63.8) | 163 | (47.2) | 13 | (48.1) | 71 | (42.0) |
| With no adverse experiences | 15 | (33.3) | 155 | (44.9) | 17 | (36.2) | 182 | (52.8) | 14 | (51.9) | 98 | (58.0) |
| With serious adverse experiences | 2 | (4.4) | 7 | (2.0) | 1 | (2.1) | 1 | (0.3) | 0 | (0.0) | 1 | (0.6) |
| Who died | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Discontinued due to an adverse experience | 5 | (11.1) | 24 | (7.0) | 3 | (6.4) | 14 | (4.1) | 1 | (3.7) | 4 | (2.4) |
| Discontinued due to a serious adverse experience | 1 | (2.2) | 7 | (2.0) | 1 | (2.1) | 0 | (0.0) | 0 | (0.0) | 1 | (0.6) |

Comments:

In this particular study, there are numerically more myocardial infarctions in the rofecoxib group, compared with nabumetone and placebo. There are also more cardiovascular adverse experiences and discontinuations due to cardiovascular adverse experiences in the rofecoxib group; this can be partly accounted for the incidence of hypertension. As with 085, this study has a smaller sample size and cardiovascular event rate compared with VIGOR.

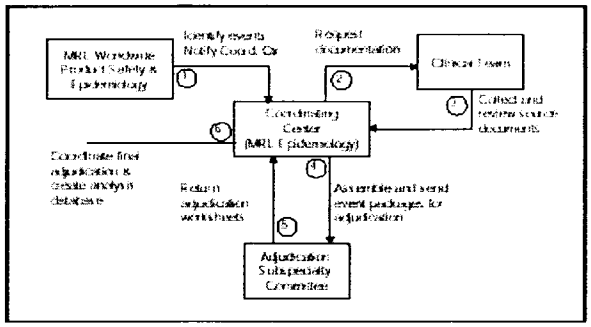
**ISSUES & COMMENTS:**

**Specific issues requested by the Division:**

1. **Adjudication Criteria and results of Adjudication in the VIGOR study (088c):**
   See Section on Adjudication (page 10). The criteria for adjudication appear to be adequate and the results appear to be balanced. In order to ascertain whether or not the adjudication was done in a blinded manner, it would be important to determine the timing of the Vascular Events Committee (i.e., when the committee was formed).

Figure C-1

Overview of Cardiovascular Event Surveillance, Monitoring, and Adjudication




2. **Evaluation of CV events in other rofecoxib studies that allowed ASA (085 and 090):**
   See Comments on 085 and 090. Despite lower dose, smaller sample size and aspirin use, the trend is against rofecoxib.

3. **Assessment of CV thrombotic risks in this database:**
   The VIGOR study was a large study with a longer drug exposure and follow-up than the two smaller studies (085 and 090). The cardiovascular thrombotic event rates, while not high, were significantly different between the two groups; most striking were the myocardial infarction event rates. Thus, to this Medical Reviewer, there are more cardiovascular thrombotic events in the rofecoxib group than in the naproxen group; the time-to-event curves are different, favoring naproxen. This Medical Reviewer is concluding that there is an increased risk of cardiovascular thrombotic events, particularly myocardial infarction, in the rofecoxib group compared with the naproxen group. More difficult is the question of a safety signal for rofecoxib. As there is no placebo group, it will be difficult to assess the CV thrombotic risk with rofecoxib use compared with no therapy at all. The sponsor provides several hypotheses to explain the data (see below);

4. **Assessment of the sponsor's claim regarding CV risks:**

**The sponsor's claims:**

- The sponsor claims that the difference in myocardial infarctions between the two groups is primarily due to the antiplatelet effects of naproxen. This hypothesis is not supported by any prospective placebo-controlled trials

with naproxen. One can further argue that, no matter what the attribution, the results (from a cardiovascular standpoint) are favorable for naproxen.

The sponsor stated, "Overall, the risk of the combined endpoint of cardiovascular or unknown death, myocardial infarction, and cerebrovascular accident was reduced by 47% in the naproxen group relative to the rofecoxib group in the VIGOR study." The sponsor then performed an analysis of events using standard endpoint definitions from large antiplatelet trials (see page 16). In viewing this analysis, one can argue that naproxen would be the preferred drug compared to rofecoxib.

- The sponsor claims that the majority of cardiovascular events in the VIGOR study occurred in those patients who should have been on aspirin for cardioprotection. This claim has not convinced this Medical Reviewer. The VIGOR data are consistent (i.e., increased events in the rofecoxib group) even in patients who did not fall into the "aspirin-indicated" subgroup.
- The sponsor claims that patients with rheumatoid arthritis are at increased risk for cardiovascular events, either due to chronic inflammation, vasculitis, or procoagulant antibodies. There is some literature regarding the role of inflammation in atherosclerosis, and increased CRP levels have been correlated with increased cardiovascular risk--there was no analysis in this sNDA of CRP levels, vasculitis or presence of procoagulant antibodies in the VIGOR population. If one accepts that patients with rheumatoid arthritis are at increased risk for events, one is still faced with the difference in cardiovascular events between rofecoxib and naproxen. And given the premise that rheumatoid arthritis patients are at increased risk, could one not extend this argument to any patient at increased risk of cardiovascular events?
- The sponsor claims that patients with osteoarthritis and Alzheimers disease are at lower risk for cardiovascular events; rates of cardiovascular events are similar between rofecoxib and the nonselective NSAIDS. The sponsor presents safety data for rofecoxib from the osteoarthritis and Alzheimer's disease trials. However, the dose of rofecoxib and length of exposure are not explicitly stated. Also, as the sponsor notes, these events are unadjudicated.

Incidence of Unadjudicated Thrombotic Cardiovascular Serious Adverse Experiences
Comparison of Rofecoxib With Nonselective NSAIDs
Phase IIb/III Clinical Program for Rofecoxib in Osteoarthritis Patients

| | Treatment Group | N | Patients With Events | PYR[†] | Rate[‡] | Relative Risk[§] Estimate | 95% CI |
|---|---|---|---|---|---|---|---|
| Unadjudicated thrombotic cardiovascular serious adverse experiences | Rofecoxib | 3357 | 34 | 1657 | 2.05 | 1.09 | (0.60, 1.99) |
| | Nonselective NSAIDs | 1564 | 16 | 706 | 2.27 | | |

[†] Patient-years at risk.
[‡] Per 100 PYR.
[§] Relative risk of nonselective NSAIDs with respect to rofecoxib from Cox model stratified by protocol where the number of cases is at least 11, otherwise relative risk is ratio of rates and p-value is from discrete logrank distribution.
[120]

Incidence of Unadjudicated Thrombotic Cardiovascular Serious Adverse Experiences
Comparison of Rofecoxib to Placebo
Phase IIb/III Clinical Program for Rofecoxib in Osteoarthritis Patients

| | Treatment Group | N | Patients With Events | PYR[†] | Rate[‡] | Relative Risk[§] Estimate | 95% CI |
|---|---|---|---|---|---|---|---|
| Unadjudicated thrombotic cardiovascular serious adverse experiences | Rofecoxib | 1701 | 9 | 363 | 2.48 | 1.05 | (0.27, 4.02) |
| | Placebo | 514 | 3 | 127 | 2.36 | | |

[†] Patient-years at risk.
[‡] Per 100 PYR.
[§] Relative risk of placebo with respect to rofecoxib from Cox model stratified by protocol where the number of cases is at least 11, otherwise relative risk is ratio of rates and p-value is from discrete log-rank distribution.
[120]

- The sponsor recommends use of low-dose aspirin in conjunction with rofecoxib, in those at risk for cardiovascular events. However, the "trade-off" with low-dose aspirin use might be a rise in GI toxicity, and a loss of the GI safety benefit offered by selective COX-2 inhibition[7]. The benefit of a rofecoxib-aspirin combination over naproxen is unclear and would at least require further study.
  - It is also conceivable that low-dose aspirin combined with rofecoxib might require further study in terms of dose-response and additivity; the question of drug development as a combination would need to be discussed within your Division.

5. **Suggest labeling that would properly address CV risks:** It is difficult to write labeling at this point.

[7] In one 2849 patient double-blind, controlled trial where patients were randomly assigned to 81 mg, 325 mg, 650 mg, or 1300 mg aspirin daily for 3 months, gastrointestinal bleeding appeared to be unrelated to dose. Taylor DW et. al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy; a randomised controlled trial. *Lancet* 1999; 353: 2179-2184.

As discussed with Dr. Villalba, we will be glad to discuss labeling with your Division. It would be difficult to imagine inclusion of VIGOR results in the rofecoxib labeling without mentioning cardiovascular safety results in the study description as well as the Warnings sections.

**RECOMMENDATIONS:**

- Your Division will need to consider the risks vs. benefits of rofecoxib and naproxen. We will be glad to discuss this issue further with you.
- We would like to see further analysis of the updated Time-to Event table to answer the following questions: 1. How significant is this table; 2. What event rate is needed to detect a significant difference between rofecoxib and naproxen.
- You should look at the VIGOR congestive heart failure results to clarify whether these events are related to edema, hypertension, or thrombotic events. You might ask the sponsor for further clarification.
- You might consider looking at celecoxib data to evaluate whether there is evidence of a class effect.
- It would be helpful if the sponsor could provide further cardiovascular safety data regarding long-term (>2 month) exposure of rofecoxib 50 mg and above, both in rheumatoid arthritis and non-rheumatoid arthritis populations.
- As we have discussed, OPDRA should be asked to look at cardiovascular safety data for the COX-2 inhibitors.

cc:
Original to NDA 21-042
HFD-550/Villalba
HFD-550/Cook
HFD-110
HFD-110/Targum
HFD-110/Stockbridge
HFD-110/Lipicky

APPEARS THIS WAY
ON ORIGINAL

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**Memorandum**

**DATE:** December 8, 2000

**FROM:** Shari L. Targum, M.D., Medical Officer
Division of Cardio-Renal Drug Products, HFD-110
**THROUGH:** Norman Stockbridge, M.D., Ph.D., Team Leader
Division of Cardio-Renal Drug Products, HFD-110
Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products, HFD-110
**TO:** Sandra Cook, Project Manager, Division of Anti-Inflammatory Drug Products, HFD-550
Maria L. Villalba, MD, Medical Officer, Division of Anti-Inflammatory Drug Products, HFD-550

**SUBJECT:** Consultation NDA 21-042, S-007
Review of cardiovascular safety database

**NAME OF DRUG:** Rofecoxib (MK-0966)
**TRADE NAME:** VIOXX™
**FORMULATION:** tablets

**RELATED APPLICATIONS:** A submission for efficacy in rheumatoid arthritis is planned for the end of 2000.
**APPROVED INDICATIONS:** Acute pain (50 mg/day for up to 5 days) and osteoarthritis (12.5 and 25 mg/day)
**SPONSOR:** MERCK Research Laboratories

**DOCUMENTS AVAILABLE FOR REVIEW:**
1. NDA 21-042, S-007 (electronic document room); 2. Prior Consultation from HFD-110 (Dr. Pelayo), 4/30/99;
3. Primary Medical Review (Dr. Villalba), NDA 21-042; 4. Rodriguez LA et. al: Differential Effects of Aspirin and Non-Aspirin Nonsteroidal Antiinflammatory Drugs in the Primary Prevention of Myocardial Infarction in Postmenopausal Women. *Epidemiology* 2000; 11 (4):382-387.

**DATE CONSULT RECEIVED:** August 16, 2000
**DATE CONSULT COMPLETED:** December 8, 2000

The purpose of this consultation is to address a concern regarding risk of cardiovascular events with the use of rofecoxib, a selective COX-2 inhibitor. The Medical Reviewer, HFD-550, had five specific questions (see Attached Consultation) for the Cardio-Renal Division; these questions will be addressed under Issues and Comments, page 30.

# BACKGROUND:

Prostaglandins have a role in a wide variety of processes, including inflammation and pain; inhibition of prostaglandin production by cyclooxygenase (COX) inhibitors such as aspirin and nonsteroidal anti-inflammatory has been an important means of providing analgesic and anti-inflammatory benefits.

Cyclooxygenases, enzymes that metabolize arachidonic acid to produce prostaglandins, are subdivided into two isoforms:

1. COX-1, constitutively expressed in most cells, which results in the production of homeostatic prostaglandins that maintain GI mucosal integrity as well as renal blood flow ; in addition, COX-1, found in platelets, mediates production of thromboxane A2, a prostaglandin that promotes vasoconstriction and well as platelet activation and aggregation.

2. COX-2, purportedly inducible[1] in selected tissues, which results in the production of prostaglandins at inflammatory sites as well as prostacyclin ($PGI_2$), a vasodilator and inhibitor of platelet aggregation. Platelets do not express COX-2; COX-2 inhibition, therefore, would not be expected to directly affect platelet function. However, COX-2 inhibition might, by suppressing prostacyclin production, "inhibit the inhibitor" of platelet aggregation.

Selective COX-2 inhibition would thus have the theoretical benefit of analgesia and decreased inflammation with fewer GI-related side effects (decreased bleeding, ulcers); however, there would also exist a theoretical concern about PGI inhibition and unopposed thromboxane production, leading to an increase in cardiovascular thrombotic events.

Evidence for inhibition of prostacyclin but not thromboxane can be found in this sNDA (CV Events Analysis, pages 79-84; see also Appendix A), where the lack of COX-2 effects on bleeding time and ex vivo platelet aggregation are noted.

It should be noted that there may be aspirin effects, other than thromboxane A2 and/or prostacyclin effects, that might alter the atherosclerotic process. While prostaglandin (thromboxane A2) inhibition has been the major mechanism of aspirin's cardiovascular benefit, it has been proposed that aspirin may also act as an antioxidant, protecting LDL from oxidative modification and improving endothelial dysfunction in atherosclerotic vessels [2]. There are currently two marketed COX-2 inhibitors: celecoxib and rofecoxib. As mentioned above, rofecoxib is approved for osteoarthritis (12.5-25 mg per day) and acute pain (50 mg/day for up to 5 days). Doses of rofecoxib up to 500 mg have been studied in man[3]. However, most of the exposure for $\geq$ 6 months has been to 12.5 and 25 mg daily; according to a prior NDA review, 272 patients have received rofecoxib 50 mg daily for $\geq$ 6 months[3]; at doses of 25-50 mg per day, hypertension, edema, and increased serum creatinine have been noted[4] in a dose-dependent manner.

The Sponsor has submitted sNDA-007 with the apparent goal of establishing a GI safety claim, i.e., reduction in GI bleeding and ulcers, for rofecoxib. An sNDA for an efficacy claim in the treatment of rheumatoid arthritis is planned for the end of 2000.

### Methology:

The focus of this review was on the cardiovascular safety of rofecoxib (MK-0966) 50 mg daily in patients with rheumatoid arthritis. To accomplish this review, the Medical Reviewer used the electronic version of the sNDA submission as well as prior reviews (see footnotes) for a reference database. Unless otherwise indicated, all analyses utilized will be taken from the Sponsor's analyses and have not been corroborated by statisticians from HFD-110.

On October 13, 2000, the sponsor submitted a safety update which included 11 additional patients referred for adjudication of cardiovascular serious adverse experiences after February 10, 2000, the prespecified cut-off date in

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[1] According to a prior consult from HFD-110 (Dr. Pelayo), there may be constitutive expression of COX-2 in the kidney.

[2] Awtry EH and Loscalzo J. Aspirin. *Circulation*. 2000; 101: 1206-1218.

[3] Prior Medical Officer (Dr. Villalba) review; NDA 21-042/21-052 (5/17/99): Safety Review: page 74.

[3] vide supra.

[4] Prior consult from HFD-110 (Dr. Pelayo) to HFD-550, completed April 30, 1999.

the original safety report. Where possible, the Medical Reviewer will present data from the safety update rather than the original report.

### *Protocol 088-04 VIGOR (VIOXX GI Outcomes Research)*

**Title:** A Double-Blind, Randomized, Stratified, Parallel-Group Study to Assess the Incidence of PUBs[5] During Chronic Treatment With MK-0966 or Naproxen in Patients With Rheumatoid Arthritis: U.S. Cohort. (VIGOR)

Study dates: January 6, 1999 (first patient in) - March 17, 2000 (last patient out)
Number of sites: 301 (multinational)

Primary Objectives:

1. To determine the relative risk of confirmed PUB (Perforation, Ulcers, Bleeding) in patients taking MK-0966 50 mg daily compared to patients in the group taking naproxen 1000 mg/day.
2. To study the safety and tolerability of MK-0966 in patients with rheumatoid arthritis.

Study Design:

This was a Phase III parallel-group, double-blind study conducted under in-house blinding procedures. There were 2 protocols, 088 (US) and 089 (multinational); however the study was conducted as a single study with a projected total of 7000 patients, with approximately 3500 from the U.S. Treatment duration was partially event-driven, i.e. determined by the need to observe at least 120 confirmed PUBs and and at least 40 confirmed complicated PUBs, or for the minimum duration of treatment to be 6 months, whichever came last.

Patients were eligible if they were 50 years or older with rheumatoid arthritis and felt to require NSAID therapy for at least 1 year; patients 40 to 49 years on chronic oral steroids were also eligible. Patients were stratified by a history of a peptic ulcer, upper GI bleeding or perforation versus those without this history.

**The use of low-dose aspirin was not allowed in this study; patients requiring aspirin for cardioprotection were excluded.** Other "cardiac-related" exclusions: angina or congestive heart failure with symptoms at rest or minimal activity, myocardial infarction or coronary bypass grafting within 1 year, stroke or transient ischemic attack within 2 years, uncontrolled hypertension.

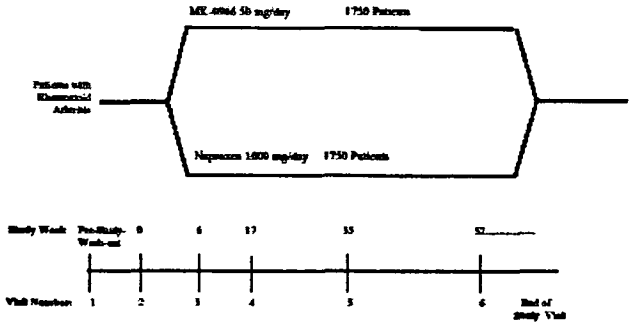
Those eligible were randomized to MK-0966 50 mg per day or naproxen 500 mg 2 times a day in a blinded fashion (double-dummy technique); there was no placebo arm. The primary endpoint was occurrence of PUBs. Other endpoints were related to efficacy or GI safety and included: complicated PUBs, discontinuation due to lack of efficacy, Patient Global Assessment of Disease Activity, and Investigator Global Assessment of Disease Activity.

Prespecified subgroups (for analysis) included: prior history of PUB, age, gender, race, and study region.



[5] **PUB** refers to gastrointestinal (GI) perforation, gastric outlet obstructions, complicated ulcers, severe upper GI bleeding.

STUDY DESIGN



Besides all serious adverse experiences and those leading to study discontinuation, prespecified adverse experiences included those related to: digestive system, hypertension, edema, renal (clinical or laboratory adverse experiences), hepatic (clinical or laboratory adverse experiences), and congestive heart failure;

Patients who discontinued were to have a discontinuation visit within 48 hours of their dropping from the study. In addition, those who discontinued were contacted 14 days after the last day of treatment for a safety follow-up. They were also contacted 45 days after the last day of treatment and at the end of study to specifically check for a GI adverse experience.

A Protocol Amendment on 9/2/99 removed the requirement for a 14 day follow up phone call for those completing the study.

Committees:

Steering Committee provided overall direction of the trial and was responsible for the trial's conduct. In the protocol, this committee was to be blinded to the results–though the DSMB (see below) had the option of "unblinding" some members of the Steering Committee to certain aspects of the data.

Executive Committee decided on practical issues during the trial and advised the Steering Committee.

Advisory Committee would meet with the DSMB, discuss recommendations to terminate the study or amend the protocol, and discuss these recommendations with the Steering Committee.

End Point Classification Committee was to define and review all PUBs (per protocol).

Case Review Committee was to have final blinded adjudication for all potential endpoints. This committee consisted of three voting clinicians, of whom at least two were gastroenterologists.

Data and Safety Monitoring Board (DSMB) monitored this trial for beneficial or adverse effects; except for a nonvoting Merck statistician, members of this committee were to be independent from the Sponsor, investigators, and patients.

A blinded, external Vascular Event Committee (VEC), containing three separate subspecialty committees (cardiac, cerebrovascular, and peripheral), existed for surveillance, monitoring, and adjudication of vascular events occurring in COX-2 inhibitor trials.

The Vascular Events Monitoring and Adjudication SOP can be found in the protocol: Category 3, Appendix 6 under 088c (sNDA, P088c: Appendix 3.2.1, pdf. Page 1681), dated August 30, 1999. Your Division, HFD-550, has been asked to clarify whether the Vascular Event Committee was prespecified, or created in response to a safety concern). The DSMB minutes begin in October, 1999.

DSMB: Minutes of the VIGOR DSMB meetings on October 4, 1999, November 18, 1999, and December 22, 1999 can be found in sNDA S-007: P088C: Appendix 3.9.1 (pdf pages 2937-2952).

The October 3, 1999 meeting was convened to discuss the first interim analysis of the VIGOR trial; at this time there was no specific mention of cardiovascular adverse events.

During the November 18, 1999 meeting, discussion focused on the "excess deaths and cardiovascular adverse experiences in Group A compared to Group B" (52 versus 29 serious cardiovascular events, respectively). In this report, there were 40 and 17 patients that discontinued the study because of cardiovascular adverse events in Groups A and B, respectively. In addition, a mean increase in systolic blood pressure ( 4 mm Hg) was noted in Group A and a corresponding increase in hypertension adverse events, compared to little or no change in Group B. It was noted

that this trial was unable to distinguish between a potentially harmful effect of Treatment A and a cardioprotective effect of Treatment B; in addition, the event rates were small. DSMB members expressed concern but the trial was allowed to continue. Additional analyses (Cox model, subdividing by those with underlying cardiac disease) were planned. An additional non-endpoint safety analysis was planned with a December 1 cutoff.

In a December 20, 1999 letter to the sponsor, the DSMB recommended development of a separate analysis plan for adjudicated events in the VIGOR study. This letter specifically stated that "it will be important that these events be adjudicated blinded." One concludes from this statement that the DSMB received unadjudicated adverse event data.

In the December 22, 1999 meeting the additional analysis was presented; it was noted that (as expected) a higher rate of events occurred in the higher risk patients in both treatment groups. No member felt that the trial should be stopped; members expressed relief that the effect might be "due to cardioprotective effects of Treatment B." At the time, no cardiovascular analysis plan was in place for VIGOR or VIOXX; it was again suggested that the analysis plan be developed prior to unblinding.

Results:

**Patient Disposition:**

The following table represents patient accounting, as noted by the sponsor. No meaningful differences in patient disposition are noted between the two treatment groups. Approximately 29% of patients did not complete this trial. The most common reason for discontinuation was the occurrence of a clinical adverse experience. There appear to be no meaningful differences between the two treatment groups in percentage discontinuing the trial and the overall reasons for discontinuation. Slightly more patients in the rofecoxib group were discontinued due to laboratory adverse experience and protocol deviations.

| | Patient Accounting | | | | | |
|---|---|---|---|---|---|---|
| | Rofecoxib 50 mg n (%) | | Naproxen 1000 mg n (%) | | Total n (%) | |
| TOTAL PATIENTS | 4047 (100.0) | | 4029 (100.0) | | 8076 (100.0) | |
| COMPLETED TRIAL | 2862 | (70.7) | 2880 | (71.5) | 5742 | (71.1) |
| DISCONTINUED TRIAL | 1185 | (29.3) | 1149 | (28.5) | 2334 | (28.9) |
| Clinical adverse experience | 645 | (15.9) | 636 | (15.8) | 1281 | (15.9) |
| Laboratory adverse experience | 22 | (0.5) | 12 | (0.3) | 34 | (0.4) |
| Lack efficacy | 256 | (6.3) | 263 | (6.5) | 519 | (6.4) |
| Lost to follow-up | 6 | (0.1) | 4 | (0.1) | 10 | (0.1) |
| Patient discontinued for other | 27 | (0.7) | 30 | (0.7) | 57 | (0.7) |
| Patient moved | 17 | (0.4) | 16 | (0.4) | 33 | (0.4) |
| Patient withdrew consent | 138 | (3.4) | 130 | (3.2) | 268 | (3.3) |
| Protocol deviation | 74 | (1.8) | 58 | (1.4) | 132 | (1.6) |
| Data Source: [4.7] | | | | | | |

(Source: Study Report 088c: pdf. page 92. Original submission: 6/29/00)

## Drug Exposure:

As noted below, patients were followed for a mean of 8.0 months. There appear to be no meaningful differences in the two treatment groups in the duration of follow-up or the number of patients exposed to study drugs.
(Source: 088c Clinical study report pdf. page 93. Original submission: 6/29/00)

| Time in Study† | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Treatment | | | Duration of Follow-Up (Months) | | | |
| Cohort | Group | N | Mean | SD | Median | Range | Inter-Quartile Range |
| Overall | Rofecoxib | 4047 | 8.0 | 3.1 | 9.0 | 0.5 to 13.0 | 7.5 to 10.1 |
| | Naproxen | 4029 | 8.0 | 3.1 | 9.0 | 0.5 to 12.7 | 7.6 to 10.1 |
| | Total | 8076 | 8.0 | 3.1 | 9.0 | 0.5 to 13.0 | 7.6 to 10.1 |
| U.S. | Rofecoxib | 1748 | 7.5 | 3.6 | 8.5 | 0.5 to 13.0 | 4.4 to 10.3 |
| | Naproxen | 1750 | 7.5 | 3.5 | 8.5 | 0.5 to 12.7 | 4.4 to 10.3 |
| | Total | 3498 | 7.5 | 3.6 | 8.5 | 0.5 to 13.0 | 4.4 to 10.3 |
| Multi-national | Rofecoxib | 2299 | 8.4 | 2.7 | 9.2 | 0.5 to 12.3 | 8.0 to 10.0 |
| | Naproxen | 2279 | 8.4 | 2.6 | 9.2 | 0.5 to 12.2 | 8.1 to 10.0 |
| | Total | 4578 | 8.4 | 2.7 | 9.2 | 0.5 to 12.3 | 8.0 to 10.0 |
| † | Up to 14 days past discontinuation. | | | | | | |

| Number of Patients in the Study at Different Time Points† | | | | |
|---|---|---|---|---|
| | | Rofecoxib | Naproxen | Total |
| | | (N=4047) | (N=4029) | (N=8076) |
| Month | | n (%) | n (%) | n (%) |
| | 2 | 3645 (90.1) | 3647 (90.5) | 7292 (90.3) |
| | 4 | 3407 (84.2) | 3395 (84.3) | 6802 (84.2) |
| | 6 | 3181 (78.6) | 3173 (78.8) | 6354 (78.7) |
| | 8 | 2806 (69.3) | 2800 (69.5) | 5606 (69.4) |
| | 9 | 2026 (50.1) | 2039 (50.6) | 4065 (50.3) |
| | 10 | 1072 (26.5) | 1074 (26.7) | 2146 (26.6) |
| | 11 | 440 (10.9) | 432 (10.7) | 872 (10.8) |
| | 12 | 57 (1.4) | 60 (1.5) | 117 (1.4) |
| †The number of patients at each time point indicated represents the number of patients completing the previous time point and at risk at the beginning of the indicated time period. | | | | |
| Duration of observation includes 14 days past date of discontinuation. | | | | |
| (Source: 088c Study Report pdf. page 94. 6/29/00) | | | | |

## Baseline characteristics:

Baseline characteristics between the two treatment groups revealed no meaningful differences in age, weight, height, ethnic group, study region, alcohol use, duration of RA, ARA status, smoking history, or history of cardiac disease.

The study population was mostly female (approx. 80%), mainly (over 70%) under 65, and mainly (approx. 68%) Caucasian. About 43% of the total population came from the U.S. Almost half of the total population had a history of "cardiac disease"(it is unclear how this parameter was defined) and about half had a history of any cardiac risk factor; however, less than 6% had a history of atherosclerotic cardiovascular disease (see below, Table C-1, Baseline Cardiovascular Demographics). About 82% had a history of prior NSAID use (for RA or other reasons) with no difference between the two treatment groups.

| Baseline Patient Characteristics by Treatment Group | | | |
|---|---|---|---|
| | | | |
| Treatment Group | N | Mean (SD) | |
| **Age (Years)** | | | |
| Rofecoxib | 4047 | 58.0 | (9.5) |
| Naproxen | 4029 | 58.2 | (9.6) |
| Total | 8076 | 58.1 | (9.5) |
| **Weight (kg)** | | | |
| Rofecoxib | 4045 | 72.2 | (17.7) |
| Naproxen | 4027 | 71.9 | (17.0) |
| Total | 8072 | 72.1 | (17.3) |
| **Height (cm)** | | | |
| Rofecoxib | 4026 | 161.8 | (10.2) |
| Naproxen | 4010 | 161.8 | (10.0) |
| Total | 8036 | 161.8 | (10.1) |

Source: Sponsor: 088c: pdf. page 98. Original submission 6/29/00.

| | Rofecoxib | | Naproxen | | Total | |
|---|---|---|---|---|---|---|
| Baseline Demographics | (N=4047) | | (N=4029) | | (N=8076) | |
| | n | (%) | n | (%) | n | (%) |
| **Gender** | | | | | | |
| Female | 3223 | (79.6) | 3215 | (79.8) | 6438 | (79.7) |
| Male | 824 | (20.4) | 814 | (20.2) | 1638 | (20.3) |
| **Ethnic Group** | | | | | | |
| White | 2761 | (68.2) | 2750 | (68.3) | 5511 | (68.2) |
| Black | 207 | (5.1) | 202 | (5.0) | 409 | (5.1) |
| Asian | 101 | (2.5) | 85 | (2.1) | 186 | (2.3) |
| Hispanic | 501 | (12.4) | 516 | (12.8) | 1017 | (12.6) |
| Multi-racial | 464 | (11.5) | 466 | (11.6) | 930 | (11.5) |
| Other | 13 | (0.3) | 10 | (0.2) | 23 | (0.3) |
| **Study Region** | | | | | | |
| U.S. | 1748 | (43.2) | 1750 | (43.4) | 3498 | (43.3) |
| Multinational | 2299 | (56.8) | 2279 | (56.6) | 4578 | (56.7) |
| **Age Group** | | | | | | |
| <40 | 10 | (0.2) | 11 | (0.3) | 21 | (0.3) |
| **History of Cardiac Disease** | | | | | | |
| Yes | 1884 | (46.6) | 1838 | (45.6) | 3722 | (46.1) |
| No | 2163 | (53.4) | 2191 | (54.4) | 4354 | (53.9) |
| **Smoking Status** | | | | | | |
| Unknown | 1 | (0.0) | 0 | (0.0) | 1 | (0.0) |
| Never Smoked | 2128 | (52.6) | 2150 | (53.4) | 4278 | (53.0) |
| Ex-Smoker | 1128 | (27.9) | 1100 | (27.3) | 2228 | (27.6) |
| Current Smoker | 790 | (19.5) | 779 | (19.3) | 1569 | (19.4) |
| **Number Cigarettes/24 Hours** | | | | | | |
| <11/day | 404 | (51.1) | 409 | (52.5) | 813 | (51.8) |
| 11 to 20/day | 271 | (34.3) | 252 | (32.3) | 523 | (33.3) |
| >20/day | 115 | (14.6) | 118 | (15.1) | 233 | (14.9) |

Source: 088c: pdf. Pages 99- 100. Original submission 6/29/00.

Baseline cardiac risk factors are presented ( next page):
There appear to be no meaningful differences between the two treatment groups in age, gender, past cardiovascular history, and cardiac risk factors.

| Baseline Cardiovascular Demographics in Rheumatoid Arthritis Patients Enrolled in the VIGOR Study (CV events analysis: original table, 6/29/00) | Rofecoxib (N=4047) | | Naproxen (N=4029) | |
|---|---|---|---|---|
| Demographic | n | (%) | n | (%) |
| | | | | |
| **Age** | | | | |
| Percent <65 Years Old | 3050 | (75.4) | 2959 | (73.4) |
| Percent ≥65 Years Old | 997 | (24.6) | 1070 | (26.6) |
| **Past Cardiovascular History** | | | | |
| Past History of Atherosclerotic Cardiovascular Disease | 238 | (5.9) | 216 | (5.4) |
| Coronary Artery Disease | 171 | (4.2) | 153 | (3.8) |
| Myocardial Infarction | 57 | (1.4) | 50 | (1.2) |
| Cerebrovascular Disease | 26 | (0.6) | 25 | (0.6) |
| Cerebrovascular Accident | 12 | (0.3) | 16 | (0.4) |
| Peripheral Arterial Disease | 56 | (1.4) | 49 | (1.2) |
| **Cardiovascular Risk Factors** | | | | |
| Any Cardiovascular Risk Factor | 2047 | (50.6) | 1988 | (49.3) |
| Hypertension | 1217 | (30.1) | 1168 | (29.0) |
| Diabetes Mellitus | 240 | (5.9) | 254 | (6.3) |
| Current Smoker | 790 | (19.5) | 779 | (19.3) |
| Hypercholesterolemia | 343 | (8.5) | 293 | (7.3) |
| | | | | |
| **Indication for Aspirin Therapy** | | | | |
| Aspirin Therapy Indicated† | 170 | (4.2) | 151 | (3.7) |

† Patients with past medical histories that met criteria for chronic vascular-protective aspirin therapy (past history of either cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable or stable angina, coronary artery bypass graft surgery, or percutaneous coronary interventions).
[P088C]

In the October 13, 1999 Safety Update, the Baseline Cardiovascular Demographics were further subdivided by the sponsor into US and Multinational cohorts. This reviewer found no meaningful differences between the two treatment groups in the various baseline characteristics and cardiac risk factors. These tables can be found in S-007, 10-13-2000 Safety Update Report, Attachment 5, pdf. Pages 58-59.

Dropouts:

There were 1131 and 1032 patients in the rofecoxib and naproxen groups, respectively, that discontinued the study for any reason other than the primary endpoint. The rates of discontinuation were 42.6 and 38.9 per 100 patients years, respectively. The relative risk was 1.10 (95% CI: 1.01, 1.19; p=0.033). This difference appears to be due to an increase in discontinuations due to clinical adverse experiences other than PUBs.

The findings below are consistent with a previous safety review from HFD-110 which found a dose-related increase in hypertension and edema in rofecoxib.[6] There is a numerical increase in congestive heart failure adverse experiences in the rofecoxib group; this trend was not significant. It is unclear whether this trend (or this patient population) is related to, or is separate from, the edema-related adverse experiences. It is also unclear whether the congestive heart failure is related to other events, such as hypertension or ischemia. The sponsor should be asked to clarify these respective points.

| Analysis of Prespecified Adverse Experience (AE) Categories | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Patients | | | | | |
| | Treatment | | With | | | | Relative Risk[§] | |
| Type of Adverse Experience | Group | N | Events | PYR[†] | Rates[‡] | Estimate | 95% CI[%] | p-Value |
| Serious clinical AEs | Rofecoxib | 4047 | 378 | 2611 | 14.48 | 1.21 | (1.04, 1.40) | 0.013 |
| | Naproxen | 4029 | 315 | 2631 | 11.97 | | | |
| Clinical AEs leading to discontinuation | Rofecoxib | 4047 | 643 | 2649 | 24.27 | 1.01 | (0.91, 1.13) | 0.842 |
| | Naproxen | 4029 | 635 | 2647 | 23.99 | | | |
| Discontinues due to GI AEs + abdominal pain | Rofecoxib | 4047 | 307 | 2676 | 11.47 | 0.73 | (0.63, 0.85) | <0.001 |
| | Naproxen | 4029 | 416 | 2664 | 15.62 | | | |
| Discontinues due to edema-related AEs | Rofecoxib | 4047 | 25 | 2697 | 0.93 | 1.92 | (0.98, 3.75) | 0.057 |
| | Naproxen | 4029 | 13 | 2698 | 0.48 | | | |
| Discontinues due to hypertension-related AEs | Rofecoxib | 4047 | 28 | 2697 | 1.04 | 4.67 | (1.93, 11.28) | <0.001 |
| | Naproxen | 4029 | 6 | 2699 | 0.22 | | | |
| CHF AEs | Rofecoxib | 4047 | 19 | 2696 | 0.70 | 2.11 | (0.96, 4.67) | 0.065 |
| | Naproxen | 4029 | 9 | 2698 | 0.33 | | | |

[†] Patient-years at risk.
[‡] Per 100 PYR.
[§] Relative risk of rofecoxib with respect to naproxen from Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates and
p-value is from discrete log-rank
distribution.
[%] Confidence interval.
Data Source: [4.3]
Adapted from 088c: Table 44. pdf. Pages 152-153. Original submission 6/29/00.

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[6] See prior consult from HFD-110 (Dr. Pelayo) to HFD-550, completed April 30, 1999.

## Adjudication:

| Summary of Analysis of Cardiovascular Serious Adverse Experiences Referred for Adjudication | | | | | | | |
|---|---|---|---|---|---|---|---|
| VIGOR Study in Patients With Rheumatoid Arthritis (10/13/00 Safety Update) | | | | | | | |
| | Updated Application Data | | | | | | |
| | | | | | | | |
| | Treatment | | Patients With | | | Relative Risk | |
| Event Category | Group | N | Events | PYR[†] | Rates[‡] | Estimate | 95% CI |
| | | | | | | | |
| All unadjudicated thrombotic cardiovascular | Rofecoxib | 4047 | 64 | 2695 | 2.37 | | |
| serious adverse experiences | Naproxen | 4029 | 32 | 2696 | 1.19 | 0.50 | (0.33, 0.76) |
| [†] Patient-years at risk. | | | | | | | |
| [‡] Per 100 PYR. | | | | | | | |
| Data Source: [Attachment 3] | | | | | | | |

Serious adverse events were evaluated by an Independent Adjudication Committee. The following table shows a disposition of those events: (Source: Safety Update 10/13/2000: pdf. page 8)

| Table 1 | | |
|---|---|---|
| | | |
| Accounting of Cardiovascular Serious Adverse Experiences That Underwent | | |
| Adjudication in the VIGOR Trial in Rheumatoid Arthritis Patients | | |
| Updated Application Data | | |
| | | |
| Serious Adverse Experience Categories | Rofecoxib | Naproxen |
| | | |
| Serious adverse experiences meeting criteria for referral to | 65 | 33 |
| adjudication | | |
| Events not meeting criteria for a thrombotic cardiovascular serious | 19 | 13 |
| adverse experience | | |
| Events adjudicated to be nonthrombotic serious adverse | 12 | 9 |
| experiences | | |
| Events adjudicated to be hemorrhagic strokes or primary | 2 | 1 |
| intracranial hemorrhage events | | |
| Events with insufficient data for adjudication | 5 | 3 |
| Events meeting criteria for a thrombotic cardiovascular serious | 46 | 20 |
| adverse experience | | |

The events excluded from adjudication appear to have been balanced; there were still about twice as many events in the rofecoxib group than in the naproxen group, whether unadjudicated or adjudicated.

The SOP for the vascular event monitoring and adjudication can be found in 088c: Category 3: Appendix 3.2.1(pdf. Pages 1678-1691. Original submission 6/29/00). The criteria for vascular event adjudication were reviewed; coronary events referred for adjudication included myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, and sudden or unexplained death. Cerebrovascular events included stroke (ischemic and hemorrhagic) and transient ischemic attack. Also considered for adjudication were venous thrombosis and pulmonary embolism.

Adjudication guidelines (088c: Appendix H: pdf. Pages 1714-1717) for myocardial infarction include 1. new pathologic Q waves in 2 contiguous leads; or 2. ischemic symptoms or ischemic repolarization changes with rising cardiac enzymes. In patients undergoing invasive cardiac revascularization, criteria are: 1. Rise in CPK-MB; or 2. Rise in Cardiac Troponin I or T; or 3. Rise in CPK (in the absence of CPK-MB); in patients following CABG, new pathologic Q waves in 2 contiguous leads within 48 hours of the procedure (otherwise the criteria are the same as for those not undergoing invasive procedures).

These criteria for myocardial infarction appear to be acceptable to this Medical Reviewer.

**Safety:**

The approach used in the cardiovascular safety evaluation for the VIGOR study included: examination of deaths, discontinuations, serious adverse events, and treatment emergent adverse events.

**Discontinuations due to serious cardiovascular adverse experiences:**

The following table lists discontinuations due to serious adverse experiences. Presumably (given the numbers) these events were unadjudicated.

| Number (%) of Patients Discontinued Due to Specific Serious Clinical Adverse Experiences by Body System (Incidence _ 0.2% in One or More Treatment Groups) | | | | |
|---|---|---|---|---|
| | Rofecoxib (N=4047) | | Naproxen (N=4029) | |
| | n | (%) | n | (%) |
| Patients with one or more adverse experience | 143 | (3.5) | 127 | (3.2) |
| Patients with no adverse experience | 3904 | (96.5) | 3902 | (96.8) |
| Cardiovascular System | 61 | (1.5) | 21 | (0.5) |
| Cerebrovascular Accident | 10 | (0.2) | 3 | (0.1) |
| Myocardial Infarction | 12 | (0.3) | 3 | (0.1) |
| Digestive System | 27 | (0.7) | 61 | (1.5) |
| Gastric Ulcer | 2 | (0.0) | 11 | (0.3) |
| Hemorrhagic Duodenal Ulcer | 4 | (0.1) | 7 | (0.2) |
| Hemorrhagic Gastric Ulcer | 2 | (0.0) | 13 | (0.3) |
| Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories. | | | | |
| Data Source: [4.3; 4.17] | | | | |

Source: Adapted from 088: Table 58: pdf. page 196. Original submission 6/29/00.

Dizziness (0.5 versus 0.2%), congestive heart failure (0.1 versus 0.0%), hypertension (0.6 versus 0.1%), myocardial infarction (0.3 versus 0.1%), unstable angina (0.1 versus 0.0%), all led to study discontinuation more frequently with rofecoxib compared with naproxen.

The following is the sponsor's analysis using standard composite endpoints seen in antiplatelet trials. The sponsor has further subdivided patients into "aspirin indicated," those with conditions where low-dose aspirin for cardioprotection was indicated, and "aspirin not indicated" categories.

It can be seen that, in the "All Patients" category, there is an increased rate of MI and stroke in the rofecoxib group compared with naproxen; in the MI group, the 95% confidence interval is significant. In the two subgroups, the composite endpoint and MI events are still favorable for naproxen and unfavorable for rofecoxib.

This analysis could lead one to conclude that naproxen, with a 51% risk reduction compared to rofecoxib, would be the preferred drug.