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Memorandum

DATE: February 1, 2001

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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.

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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 inducible¹ in selected tissues, which results in the production of prostaglandins at inflammatory sites as well as prostacyclin (PGI₂), 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 vessels². 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 man³. However, most of the exposure for ≥ 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 ≥ 6 months³; at doses of 25-50 mg per day, hypertension, edema, and increased serum creatinine have been noted⁴ 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.

Methodology:

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.

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 PUBs⁵ 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 at least 40 confirmed complicated PUBs, or for the minimum duration of treatment to be 6 months, whichever came last.

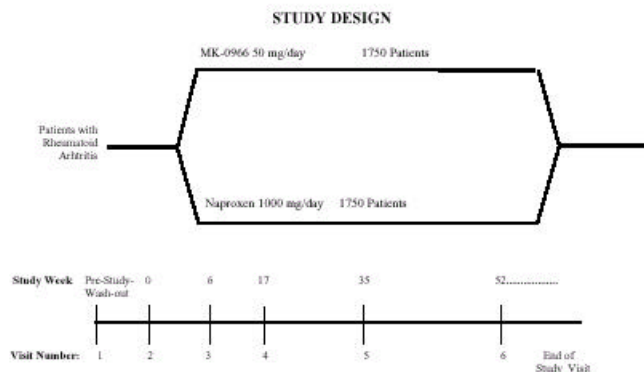
Patients were eligible if they were 50 years or older with rheumatoid arthritis and felt to require NSAID therapy for at least 1 year; patients 40 to 49 years on chronic oral steroids were also eligible. Patients were stratified by a history of a peptic ulcer, upper GI bleeding or perforation versus 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.



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		Naproxen		Total	
	50 mg		1000 mg			
	n (%)		n (%)		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 [†]							
Cohort	Treatment	N	Mean	SD	Duration of Follow-Up (Months)		
	Group				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 (N=4047)	Naproxen (N=4029)	Total (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.

Baseline Demographics	Rofecoxib (N=4047)		Naproxen (N=4029)		Total (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	
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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 serious adverse experiences	Rofecoxib	4047	64	2695	2.37		
	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 adjudication	65	33
Events not meeting criteria for a thrombotic cardiovascular serious adverse experience	19	13
Events adjudicated to be nonthrombotic serious adverse experiences	12	9
Events adjudicated to be hemorrhagic strokes or primary intracranial hemorrhage events	2	1
Events with insufficient data for adjudication	5	3
Events meeting criteria for a thrombotic cardiovascular serious adverse experience	46	20

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 \geq 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.

Event Category	Treatment	N	Number of Patients With Events	PYR [†]	Rates [‡]	Relative Risk [§]		
	Group					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]

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)

Event Category	Treatment Group	N	Patients With Events	PYR ‡	Rates ‡	Relative Risk §	
						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.

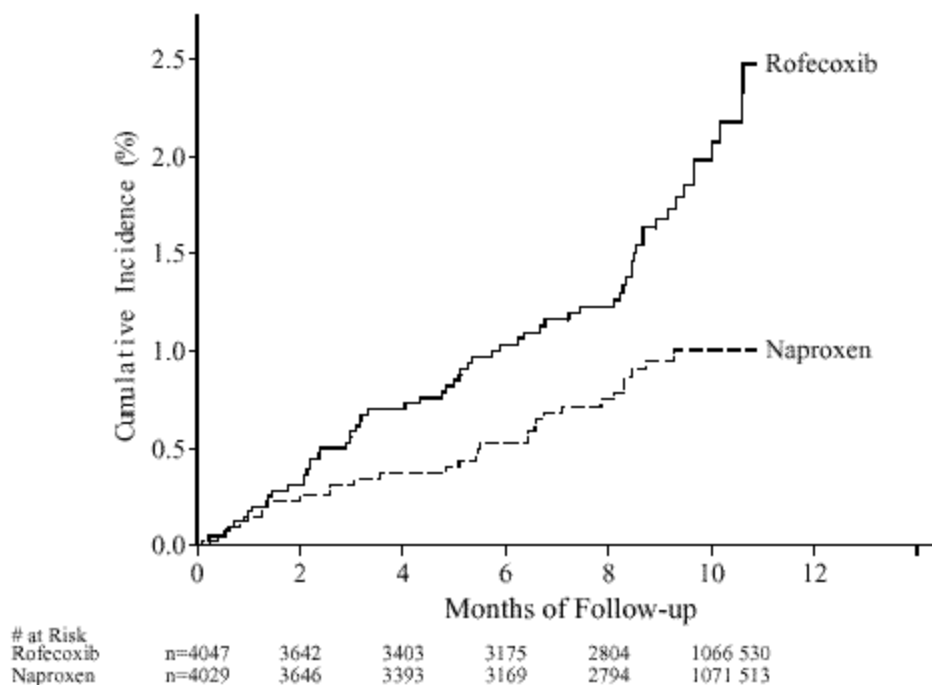
Although a patient may have had 2 or more serious adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

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.

Figure 3

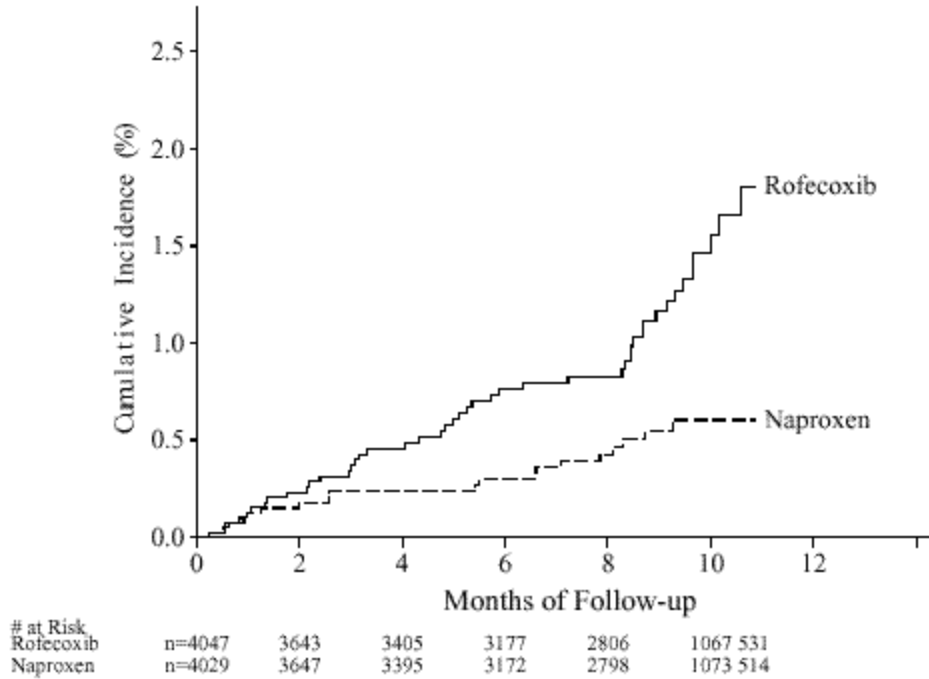
Thrombotic Cardiovascular Serious Adverse Experiences Referred for Adjudication in Rheumatoid Arthritis Patients in the VIGOR Study
Time-to-Event Plot (All Patients Randomized)
Updated Application Data



(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)

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



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				
Event	Rofecoxib		Naproxen	
	(N=4047)		(N=4029)	
	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				
VIGOR Study in Rheumatoid Arthritis Patients				
Updated Application Data				
			Patients With an Edema-Related Adverse Experience	
	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				
VIGOR Study in Rheumatoid Arthritis Patients				
Updated Application Data				
			Patients With a Confirmed Cardiovascular Serious Adverse Experience	
	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				
VIGOR Study in Rheumatoid Arthritis Patients				
Updated Application Data				
				Patients With a Hypertension-Related Adverse Experience
	Treatment Group	N	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				
VIGOR Study in Rheumatoid Arthritis Patients				
Updated Application Data				
				Patients With a Confirmed Cardiovascular Serious Adverse Experience
	Treatment Group	N	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 of 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 discontinued 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 ≤ 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.

	MK-0966 12.5 mg		Nabumetone 1000 mg		Placebo		Total 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 ($\geq 1\%$) 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)		Nabumetone 1000 mg (N=410)		Placebo (N=208)	
	n	(%)	n	(%)	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 experience of diverticulosis which began prior to randomization.

§ AN 0052 in the placebo group was counted as discontinuing due to phimosi and balaniti, 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 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		Nabumetone		Placebo		Total	
	12.5 mg (N=424)	n (%)	1000 mg (N=410)	n (%)	(N=208)	n (%)	(N=1042)	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		Low-Dose		Low-Dose							
	Aspirin (N=46)	Non-User (N=378)	Aspirin (N=57)	Non-User (N=353)	Aspirin (N=21)	Non-User (N=187)						
	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	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		Placebo		Total	
	12.5 mg		1000 mg					
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 .05 versus placebo.								
** p .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)		Nabumetone 1000 mg (N=392)		Placebo (N=196)		Total (N=978)	
	n	(%)	n	(%)	n	(%)	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)		Nabumetone 1000 mg (N=392)		Placebo (N=196)		Total (N=978)	
	n	(%)	n	(%)	n	(%)	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

Summary of Renal/Vascular Adverse Experiences †

Category	Treatment Group							
	Rofecoxib 12.5 mg (N=390)		Nabumetone 1000 mg (N=392)		Placebo (N=196)		Total (N=978)	
	n	(%)	n	(%)	n	(%)	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 Experiences	Clinical Adverse Experience Summary by Aspirin Subgroup											
	Rofecoxib 12.5 mg (N=390)				Nabumetone 1000 mg (N=392)				Placebo (N=196)			
	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)	
	n	%	n	%	n	%	n	%	n	%	n	%
Number (%) of Patients												
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:

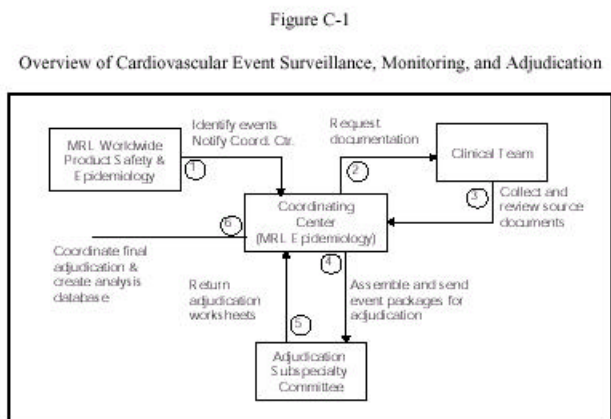
In this particular study, there are numerically more myocardial infarctions in the rofecoxib group, compared with nabumetone and placebo. There are also more cardiovascular adverse experiences and discontinuations due to cardiovascular adverse experiences in the rofecoxib group; this can be partly accounted 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).



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 inhibition⁷. 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