FDA Advisory Committee Briefing Document

NDA 21-042, s007
VIOXX Gastrointestinal Safety

February 8, 2001

NDA # 21-042 & 21-052, s007 – VIOXX GI safety

Advisory Committee Briefing Document
February 8, 2001

Table of contents

	Page
Section I. Overall Safety (Maria Lourdes Villalba, M.D.)	
1. Background	3
2. Data reviewed in this submission	4
2.1 New studies	7
2.1.1 VIGOR (088c)	7
2.1.2 Studies 085 and 090	15
2.1.3 Study 102	16
2.2 Data from original NDA (069, 058)	19
2.3 Post-marketing data	20
3. Conclusions	21
4. Recommendations	22
5. Appendix 1. Listing of deaths	24
Section II. Gastrointestinal Safety (Lawrence Goldkind, M.D.)	
Background	2
VIGOR study (088c)	5
Study design and reviewer comments	5
Conclusions regarding study design	10
Results	11
Demographics	11
GI outcome results	14
Subgroup analysis	21
Overall conclusions	28
Appendix 1. Protocol provisions	29
Section III. Cardiovascular Safety (Shari Targum, M.D.)	
Background	3
VIGOR study (088c)	4
Study 085	26
Study 090	31
Issues and comments	36
Section IV. Statistics (Qian Li, Sc. D.)	
I. Introduction	1
II. Design and Statistical Methodology	1
III. Results	5
IV. Conclusions	14

NDA 21-042/052, s007
Rofecoxib Overall Safety

1. Background

VIOXX (rofecoxib) is a non-steroidal anti-inflammatory drug (NSAID) with selective cyclooxygenase 2 (COX-2) inhibitory properties. It was approved for marketing in the U.S. in May 1999 for the treatment of acute pain in adults, dysmenorrhea and the signs and symptoms of osteoarthritis (OA).

Based on the safety profile demonstrated in the original NDA database VIOXX carries the Warnings and Precautions section of the NSAID class, including the risk of gastrointestinal (GI) bleeding, as follows:

> **WARNINGS**
>
> **Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation:**
> Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

In addition to the above paragraph, the VIOXX label states: It is unclear, at the present time, how the above rates apply to VIOXX (see CLINICAL STUDIES, Special Studies, *Upper Endoscopy in Patients with Osteoarthritis*). Safety data from two endoscopic studies in which ibuprofen was the active comparator are included under the Clinical Studies section of the label.

(Of note, the estimates of perforations, ulcers and bleeding that appear in the GI warning section of NSAID labels include ulcers associated with pain alone without the more serious complications.)

The FDA and the sponsor agreed that evidence was needed regarding clinically meaningful upper GI events as well as a large controlled database for overall safety assessment.

Based on the results of the present submission the sponsor proposes to remove the NSAID-class GI Warnings. By doing so, VIOXX would distance itself from the NSAIDs class. The sponsor proposes to include a brief paragraph describing GI risk under the Precautions section of the label.

FDA has concerns with:

- The generalizability of the findings of the VIGOR study to the general population and to NSAIDs other than the one included as an active comparator in this study.

- Remaining GI risk as evidenced by ongoing occurrence of serious complicated GI events associated with rofecoxib use in this review and in post-marketing surveillance.

- Cardiovascular safety issues raised during this review.

(Reviewer's comments in this review will appear in italics.)

2. Data reviewed in this submission

Studies reviewed under NDA 20-042/052 supplement 007 included 3 new studies and data provided in the original NDA submission. These studies are summarized in Tables 1 and 2. An additional study conducted under this NDA is summarized in Table 3.

Table 1. NDA 21-042/S007. New studies in this submission

	Design	Dz.	Treatment (mg/day)	N	ASA allowed
Study 088c "VIGOR"	"Large and simple" Multicenter, double-blind, randomized, active controlled, median 9 months f.u.	RA	Rofecoxib 50 Naproxen 1000	4027 4049	**NO**
Study 085	Multicenter, double-blind, randomized, placebo and active-controlled, six-week duration	OA	Rofecoxib 12.5 Nabumetone 1000 Placebo	424 410 208	**YES** 10-15%
Study 090			Rofecoxib 12.5 Nabumetone 1000 Placebo	390 392 196	

Table 2. Data from original NDA submission (December, 1998)

	Design	Dz.	Treatment (mg/day)	N	ASA allowed
069	Pooled studies of 6 to 86 weeks duration, including two 6-month endoscopic studies. Most patients exposed <6 months.	OA	Rofecoxib 12.5, 25 and 50 (pooled)	3357	**NO**
			Ibuprofen 2400 Diclofenac 150 Nabumetone 1000 (pooled)	1564	
			Placebo (6 weeks)	514	
058	Same as 085 and 090 but in Elderly ζ65 years	OA	Rofecoxib 12.5 Rofecoxib 25 Nabumetone 1000 Placebo	56 118 115 52	**YES** 60-70%

Table 3. Additional study

Study 102* "Advantage"	Multicenter, double-blind, randomized, active controlled, 12-week duration	OA	Rofecoxib 25 Naproxen 1000	2799 2789	**YES** 12-13%

* This study had been completed by March 2000 but not submitted as part of this supplement. Preliminary results of serious GI and CV events were submitted at FDA request.

2.1 New studies

2.1.1 Study 088c. VIOXX Gastrointestinal Outcomes Research study (VIGOR).

The objective of the VIGOR study was to determine whether VIOXX, a selective COX-2 inhibitor, would result in significant reduction in the incidence of clinically relevant GI events relative to therapy with naproxen, a non-selective COX inhibitor. The study involved approximately 4000 patients per treatment arm followed for a median time of 9 months. The use of low dose ASA for cardiovascular prophylaxis was not allowed in this study.

Rofecoxib 50 mg/day dose is the dose recommended for the treatment of acute pain and twice the highest recommended dose in osteoarthritis (OA). The dose of naproxen (500 mg bid) is the highest recommended dose for chronic use in OA and RA.

> *The exclusion of low dose ASA users seriously limits the generalizability of this study to that segment of the population.*
>
> *VIGOR was not an efficacy study. Standard RA efficacy endpoints were not measured. The efficacy of VIOXX in RA is yet to be demonstrated.*

There were no substantial differences in the baseline demographics and clinical characteristics of each treatment group. Similar number of patients used concomitant corticosteroids (approximately 56%) and methotrexate (also approximately 56%) in the rofecoxib and naproxen group, respectively).

> *The FDA has asked the sponsor to provide mean and median doses of corticosteroids used in each treatment group.*

2.1.1.1 Safety results

1. <u>Deaths</u>

There were a total of 22 deaths in the rofecoxib group and 15 in the naproxen group. A listing deaths is presented in Appendix 1.

There were 14 cardiovascular deaths, (nine and five in rofecoxib and naproxen groups, respectively). Most of the cardiovascular deaths were in patients with known cardiovascular risks.

Eight patients died of pneumonia: five in the rofecoxib group (two of them complicated with bacterial sepsis - one of them in the setting of aplastic anemia-) and three in the naproxen group.

There were five deaths due to worsening interstitial/RA lung disease (four and one in rofecoxib and naproxen groups, respectively).

Four patients died of gastrointestinal complications (3 on rofecoxib – one of them a patient with gastric carcinoma - and one on naproxen).

One patient receiving naproxen died of hepatic necrosis right after completing the study. This patient was receiving concomitant methotrexate (MTX) three times a week.

Although there were more deaths in the rofecoxib group, the small number of cases does not allow statistical comparisons.

2. <u>Serious Adverse Experiences (SAE's)</u>

There were no substantial differences in the overall incidence of SAE's (9.3% and 7.8% for rofecoxib and naproxen, respectively). Body systems with the highest incidence of SAE's were the Gastrointestinal, Cardiovascular and Musculoskeletal systems.

Table 4. Serious adverse experiences and discontinuations due to adverse experiences by body system (incidence ζ0.2%)

	Rofecoxib (N=4047) n (%)		Naproxen (N=4029) n (%)	
Number (%) of patients with one or more adverse experience	Serious 378 (9.3)	Dropouts 643 (15.9)	Serious 315 (7.8)	Dropouts 635 (15.8)
Body As A Whole/Site Unspecified	51 (1.3)	100 (2.5)	35 (0.9)	107 (2.7)
Cardiovascular System	101 (2.5)	109 (2.7)	46 (1.1)	33 (0.8)
Digestive System	48 (1.2)	292 (7.2)	97 (2.4)	392 (9.7)
Eyes, Ears, Nose, And Throat	13 (0.3)	20 (0.5)	4 (0.1)	11 (0.3)
Hemic And Lymphatic System	8 (0.2)	4 (0.1)	7 (0.2)	9 (0.2)
Hepatobiliary System	11 (0.3)	10 (0.2)	8 (0.2)	2 (0.0)
Musculoskeletal System	83 (2.1)	29 (0.7)	70 (1.7)	27 (0.7)
Nervous System	14 (0.3)	44 (1.1)	7 (0.2)	24 (0.6)
Psychiatric Disorder	7 (0.2)	3 (0.1)	3 (0.1)	10 (0.2)
Respiratory System	52 (1.3)	23 (0.6)	39 (1.0)	13 (0.3)
Skin And Skin Appendages	31 (0.8)	42 (1.0)	20 (0.5)	37 (0.9)
Urogenital System	32 (0.8)	17 (0.4)	23 (0.6)	9 (0.2)

Source: Modified from appendix 4.17.4 and 4.17.2 of 088c study report. Patients may appear under more than one category, but only once within one category.

As seen in Table 4, less than 25% of the events leading to discontinuations in the GI body system were defined as serious AE's, while most discontinuations in the CV system were defined as serious AE's. This observation raises concerns about

the possible overall safety conclusions that could be extrapolated from the GI specific results.

Of note, an effective dose has not been established for RA. The safety profile of the 50 mg dose may be relevant, as the organ specific GI safety profile may be interpreted by some as generalizable to overall safety and allowing for dose creep.

2.1 Serious Gastrointestinal events

Serious AE's related to the digestive system were observed in 48 (1.2%) and 97 (2.4%) of patients in the rofecoxib and naproxen groups, respectively.

The sponsor successfully demonstrated a risk reduction of clinically relevant GI adverse events for rofecoxib compared to naproxen.

Table 5. PUB's[1] and **complicated** PUB's[2] confirmed by the CRC[3] in the VIGOR study

	N	Events n (%)	PYR[4]	Rate[5]	Relative risk[6]		
					Estimate	95%CI	p-value
PUB's							
Rofecoxib	4047	56 (1.38)	2697	2.08	0.46	0.33, 0.64	< 0.001
Naproxen	4049	121 (3.0)	2694	4.49			
Complicated PUB's							
Rofecoxib	4047	16 (0.4)	2699	0.59	0.43	0.24, 0.78	0.005
Naproxen	4049	37 (0.92)	2698	1.37			

[1] Perforations, symptomatic ulcers and GI bleedings. [2]Excludes uncomplicated ulcers. [3]Adjudicated by the Case Review Committee. [4]Patient-years at risk. [5]Per 100 PYR. [6]Relative risk of rofecoxib compared to naproxen. Source: sponsor's tables 22, 23, 24, 26 and 31 of 088c study report.

The cumulative incidence of PUB's (perforations, symptomatic ulcers and GI bleedings) was 2.08% and 4.49% for rofecoxib and naproxen, respectively (relative risk 0.46, $p<0.001$) (Primary endpoint of the study).

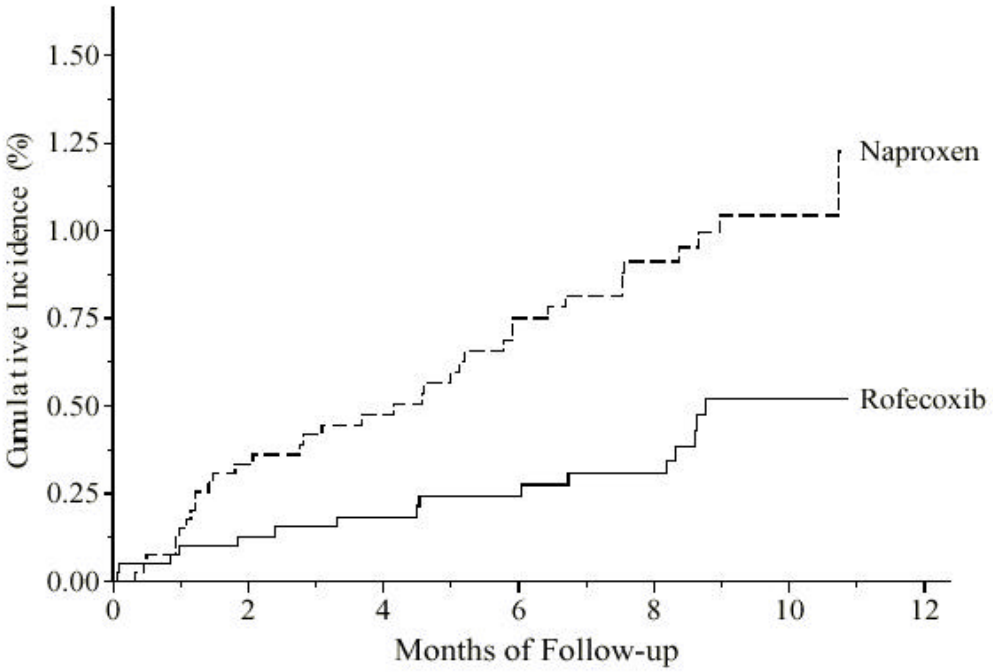
The percentage of PUB's observed in the study is very close to the risk referred to in the NSAID-class label in the general population (2-4% in patients treated for one year).

The cumulative incidence of **complicated** PUB's was 0.59% and 1.37% in the rofecoxib and naproxen groups, respectively (relative risk, 0.43, $p=0.005$) (Secondary endpoint of the study). **Complicated** PUB's include serious events of perforation, obstruction and bleeding (also referred as to POB's).

Symptomatic ulcers do not represent the same severity of endpoint as complicated PUBs. Only a small fraction of ulcers are thought to result in a clinically serious outcome. Therefore, time to event plot for ***complicated*** *PUB's is presented in Figure 1.*

For a detailed GI safety review, the reader is referred to Dr. Goldkind's review.

Figure 1. Confirmed **complicated** PUB's in the VIGOR study (secondary endpoint). Time to event plot (all patients randomized).



# at Risk							
Rofecoxib	n=4047	3644	3407	3181	2806	1072	533
Naproxen	n=4029	3646	3394	3170	2800	1074	514

Source: sponsor's Figure 5, s007 submission)

2.2 Serious Cardiovascular events

Serious cardiovascular events with the highest incidence were CV thrombotic, HTN-related and CHF-related events.

The cumulative risk of developing serious CV thrombotic events was 1.7% in the rofecoxib group compared to 0.7% in the naproxen group. (Data include eleven patients submitted with the four-month safety update).

The protocol mandated that patients with recent or significantly active cardiovascular disease be excluded from the protocol. Patients with recent MI (<1 year) or TIA/stroke

(<2 years) and patients deemed by the investigator to require prophylactic ASA or anticoagulation at the time of enrollment were excluded from the study. Patients on low dose ASA were not to stop therapy in order to enter the study.

The sponsor retrospectively identified 321 patients enrolled in this study with past medical history of cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, stable angina, coronary artery bypass surgery or percutaneous coronary intervention who might have benefited from the use of low dose ASA.

> *The validity of this retrospective identification of patients is unclear. By protocol, patients with active cardiovascular disease were excluded. The investigator's clinical judgement at the time of enrollment appears to be more relevant than a retrospective chart review.*

An analysis in this subgroup of patients retrospectively identified by the sponsor as candidates for low dose ASA showed that the risk of developing CV thrombotic events was five times higher in the rofecoxib group compared to the naproxen group (14.3% and 2.9% respectively). For those patients in whom neither prospective nor retrospective chart review suggested need for low dose ASA use, the risk was still twice in the rofecoxib group compared to the naproxen group (1.2% and 0.6%, respectively).

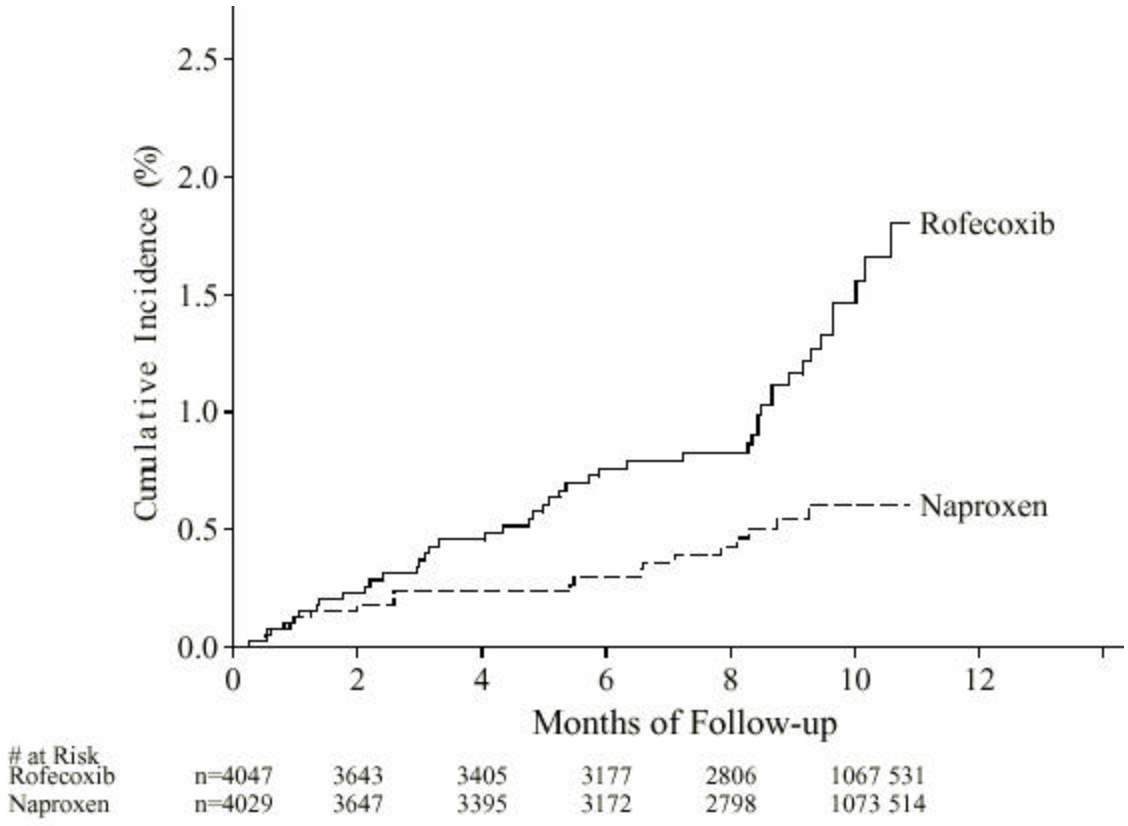
Table 6. Adjudicated thrombotic cardiovascular serious adverse experiences. Subgroup analyses by sponsor's retrospective identification of patients who may have benefited from low dose ASA.

	N	Patients with events[1] (%)	PYR[2]	Rates[3]	Relative risk[4]		
					Estimate	95%CI	p
All patients randomized							
Rofecoxib	4047	45 (1.1%)	2697	1.67	2.37	1.39 – 4.06	0.0016
Naproxen	4029	19 (0.5%)	2698	0.70			
Potential candidate for low dose ASA[5]							
Rofecoxib	170	15 (8.8%)	105	14.29	4.89	1.41 - 16.88	0.0122
Naproxen	151	3 (2.0 %)	102	2.94			
Not candidate for low dose ASA							
Rofecoxib	3877	30 (0.8%)	2592	1.16	1.88	1.03 – 3.45	0.041
Naproxen	3838	16 (0.4%)	2596	0.62			

[1]Thrombotic cardiovascular serious adverse experiences confirmed by Adjudication Committee. [2] Patient-years at risk. [3] Per 100 patients years. [4] Relative risk of rofecoxib with respect to naproxen. [5] Patients with past medical history of cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, stable angina, coronary artery bypass surgery or percutaneous coronary intervention. (Source: modified from sponsor's Table 9 of the safety update, Estimate calculated by Dr. Qian Li, stats reviewer).

A summary of adjudicated Thrombotic Cardiovascular serious adverse events in the VIGOR study is presented in Appendix 2a and 2b.

Figure 2. Confirmed Thrombotic CV serious adverse experiences in the VIGOR study. Time to event plot (all patients randomized).



Source: sponsor's Figure 1 of safety update.

The sponsor explanation for the excess of cardiovascular thrombotic events in the VIGOR study is the potent antiplatelet aggregation effect of naproxen. However, unopposed thromboxane production leading to an increase in CV thrombotic events can not be discarded as a potential explanation of the VIGOR findings.

There are several arguments against the beneficial naproxen effect being the sole explanation for these findings.

a) There are no prospective placebo-controlled trials with naproxen to support to support the assumption that naproxen transient inhibition of platelet aggregation is effective in decreasing the risk of cardiovascular events.

b) *The effect size of naproxen in reducing CV thrombotic events relative to rofecoxib in the VIGOR study (58%) exceeds the effect size of ASA compared to placebo in other trials (25-30%).*

c) *The absence of a meaningful prothombotic signal in the original NDA may be explained by the short duration and low doses of rofecoxib used in the majority of the OA database.*

   As shown in Figure 2., the cumulative incidence of CV thrombotic AE's for rofecoxib and naproxen start to diverge at approximately 3 months, but the difference increases after 8 months of follow up. Furthermore, RA is recognized as a disease associated with twice the risk of CV disease compared with OA. The population in VIGOR may be a more sensitive model for detecting the potential thrombogenic effects of selective COX-2 inhibition than a population with predominance of OA.

d) *Several other studies (085, 090 and 102) to be noted later in this review, suggest trends towards higher rates of myocardial infarction in the rofecoxib group compared to active control groups. Of note, these studies involved lower doses and duration of exposure to rofecoxib than the VIGOR trial and allowed the use of low dose ASA.*

In addition to the difference in cardiovascular thrombotic events, serious HTN-related and CHF-related events were higher in the rofecoxib group. Ten (0.2%) and one patients (0%) had a serious hypertension-related adverse experience in the rofecoxib and naproxen groups, respectively. Sixteen patients developed serious CHF-related events: 13 (0.3%) in the rofecoxib group and 3 (0.1%) in the naproxen group. Additionally, two and one patient developed pulmonary edema in the rofecoxib and naproxen group respectively.

For a detailed CV review the reader is referred to Dr. Targum's review.

2.3 Serious Musculoskeletal related AE's

Serious Musculoskeletal related AE's were relatively high in both treatment groups. They were observed in 83 (2.1%) and 70 (1.7%) of patients in the rofecoxib and naproxen groups respectively. Musculoskeletal system includes fractures, worsening RA and trauma. There were 41 (1%) and 29 (0.7%) fractures (all sites) in the rofecoxib and naproxen groups, respectively.

This is a population at increased risk for fractures. The study was not powered to detect differences in the incidence of fractures. Therefore, the difference between treatment groups may be not relevant. However, COX-2 is involved in regulation of bone metabolism and concerns have been raised about long-term effects of

some NSAIDs in the skeletal system. The sponsor is conducting a study to address the issue of long-term effects of rofecoxib in bone metabolism.

2.4 Other serious adverse experiences

Other than GI and CV safety differences, the safety profile of rofecoxib and naproxen showed a similar pattern and were consistent with those of the NSAID class. Serious AE's were consistently higher in the rofecoxib group, except for the GI system (Table 4).

3. Discontinuations due to pre-specified adverse events

Discontinuations due to NSAID-related AE's such as renal, liver, HTN and edema-related AE's were numerically higher (and some statistically significantly higher) in the rofecoxib group. CHF-related adverse events (also pre-specified) were also higher in the rofecoxib group.

Table 7: Results of pre-specified safety analyses involving NSAID-related adverse events.

Type of Adverse Experience	Treatment	N	Events	Rates	Relative Risk		
					Estimate	95%CI	p-value
Discontinued due to edema-related AEs	rofecoxib	4047	25	0.93	1.92	(0.98,3.75)	0.057
	naproxen	4029	13	0.48			
Discontinued due to hypertension-related AEs	rofecoxib	4047	28	1.04	4.67	(1.93, 11.28)	<0.001
	naproxen	4029	6	0.22			
CHF AEs	rofecoxib	4047	19	0.70	2.11	(0.96, 4.67)	0.065
	naproxen	4029	9	0.33			
Discontinued due to hepatic disease AEs	rofecoxib	4047	10	0.37	3.33	(0.92, 12.11)	0.067
	naproxen	4029	3	0.11			
Discontinued due to renal-related AE's*	rofecoxib	4047	8	0.30	1.14	(0.41, 3.15)	0.796
	naproxen	4029	7*	0.26			

Source: Modified from sponsor's tables 66 to 72, 088c study report.

** It is unclear to this reviewer whether patients AN 1824 and 2720 on naproxen were included in this analysis. These two patients had abnormal renal function in the setting of obstructive uropathy.*

4. Laboratory data

Four hundred fourteen (10.4%) and 368 (9.2%) patients presented one or more laboratory adverse experience in the rofecoxib and naproxen groups respectively. Of those, 22 patients discontinued due to laboratory AE's in the rofecoxib group compared with 12 in the naproxen group. There were only two cases of serious laboratory AE's: one case of

neutropenia and one of leukopenia and platelet decrease, both in the rofecoxib group. Both patients were taking concomitant MTX.

Of the 90 (2.2%) and 49 (1.2%) patients with liver-related (clinically and laboratory) adverse experiences in the rofecoxib and naproxen groups respectively few patients exceeded pre-defined limits of change for laboratory liver related adverse events. Four patients exceeded limits for serum ALT and 1 patient for AST (all in the rofecoxib group), defined as: in patients with normal baselines, consecutive values >3 times the ULN or 1 value >3 times the ULN associated with study drug discontinuation; in patients with abnormal baselines, consecutive values that are >2 times the baseline value and >3 times the ULN or 1 value >3 times the ULN associated with study drug discontinuation).

In this study, 0.5 and 0.3% of patients on rofecoxib and 0.2 and 0.3% of patients on naproxen had at least 1 single (nonconsecutive) AST and ALT value >3 times the ULN, respectively.

Only 4 and 3 patients in the rofecoxib and naproxen group respectively met predefined limits of change for serum creatinine (defined as consecutive values with an actual increase of ζ0.5 mg/dL and >ULN or 1 value with an increase of 0.5 mg/dL and >ULN that was associated with study drug discontinuation).

> *These criteria for LFT and creatinine predefined limit of change are more stringent than the ones used in the original NDA. In the original NDA the definition for AST and ALT predefined limit of change was a single value increased by x2 and >ULN; for creatinine it was a single value increased by z0.5 mg/dL and >ULN. Additional analyses have been requested to the sponsor.*

In general, analyses of laboratory predefined limits of change not associated with pre-specified adverse events showed no significant differences between groups. Of note, changes in sodium (hyponatremia and hypernatremia) were relatively high in both groups. The difference in the incidence of hyponatremia between rofecoxib and naproxen was statistically significant: 39 on rofecoxib (1%) and 20 on naproxen (0.5%).

5. MTX and non-MTX users

In this study, approximately 60% of patients were on MTX in each treatment group. The overall incidence of clinical adverse experiences, drug-related clinical adverse experiences, or serious clinical adverse experiences was similar for patients who took or did not take concomitant methotrexate for treatment of RA.

There were no significant differences in the overall incidence of adverse events by body system between MTX and non-MTX users for each treatment.

The only two serious laboratory events observed in the study (one of neutropenia and one leukopenia + platelet decrease) and one case of pneumonia in the setting of aplastic

anemia (a patient who died) occurred in patients taking refecoxib concomitantly with MTX.

> *This preliminary observation suggests that despite lack of apparent PK interaction between rofecoxib and MTX, rofecoxib may have increased the potential for MTX bone marrow toxicity.*

Table 8. Adverse experience summary in MTX users and non-MTX users

	MTX Users		MTX Non-users	
	Rofecoxib 50 N = 2385 %	Naproxen 1000 N = 2387 %	Rofecoxib 50 N = 1662 %	Naproxen 1000 N = 1642 %
Clinical AE's				
With one or more AE's	1716 (71.9)	1701 (71.3)	1156 (69.6)	1123 (68.4)
With serious AE's	223 (9.4)	190 (8.0)	155 (9.3)	125 (7.6)
Who died	15 (0.6)	10 (0.4)	7 (0.4)	5 (0.3)
Discontinued due to AE's	362 (15.2)	345(14.5)	281 (16.9)	290 (17.7)
Discontinued due to SAE's	84 (3.5)	74 (3.1)	59 (3.5)	53 (3.2)
Discontinued due to serious drug-related AE's	39 (1.6)	39 (1.6)	16 (1.0)	29 (1.8)
Laboratory AE's				
With one lab test post baseline	2372	2374	1634	1625
With one or more AE's	257 (10.8)	240 (10.1)	161 (9.9)	128 (7.9)
Discontinued due to adverse experiences	13 (0.5)	6 (0.3)	9 (0.6)	6 (0.4)

AE's: adverse experience. SAE: serious adverse experience. Source Appendix 4.21, Study 088c, s007.

2.1.1.1 Efficacy results

The efficacy of rofecoxib in RA remains to be demonstrated in placebo controlled studies designed for that purpose.

VIGOR was not an efficacy study. Patients were not required to meet RA flare criteria and changes in DMARD and corticosteroid therapy were allowed without restriction during the study. Standard RA efficacy endpoints such as swollen joints and tender joints were not measured.

The efficacy parameters in this study were Patient's and Investigator's Global Assessment of Disease Status, measured on the Likert scale from 0 to 4, the modified HAQ consisting of 8 questions measured on a scale of 0 to 3, and discontinuations due to lack of efficacy. There were no differences in these efficacy parameters between rofecoxib 50 mg/day and naproxen 1000 mg/day.

2.1.2. Studies 085 and 090

Studies 085 and 090 were six-week, placebo controlled studies in patients with OA. The dose of rofecoxib used in the studies was the lowest dose approved for the treatment of OA (12.5 mg/day). The dose of nabumetone (1000 mg/day) was the lowest recommended dose for OA and RA. Both studies used a 2:2:1 randomization scheme (rofecoxib/ nabumetone/placebo). Each active treatment arm involved approximately 400 patients. The studies were designed to support the efficacy of rofecoxib in patients with OA.

There were no substantial differences in the demographic and clinical characteristics at baseline in each treatment group, in each study. The studies allowed the use of prophylactic ASA. Approximately 12% of patients used ASA in these studies. The most common concomitant condition was cardiovascular; and approximately 40 % of patients had a history of HTN.

Table 9. Clinical AE summary of studies 085 and 090

	Rofecoxib 12.5 mg (N=814)	Nabumetone 1000 mg (N=802)	Placebo (N=404)
Number (%) of patients:	n (%)	n (%)	n (%)
with one or more adverse experiences	432 (53)	390 (48.6)	188 (46.5)
with serious adverse experiences	13 (1.6)	10 (1.2)	2 (0.5)
discontinued due to an adverse experience	53 (6.5)	41 (5.1)	13 (3.2)
discontinued due to a serious AE	10 (1.2)	4 (0.5)	1 (0.3)

(Source: pooled data from Table 33 and 34 of studies 085 and 090). † Considered by the investigator to be possibly, probably, or definitely drug-related.

1. Deaths. There were no deaths.

2. Serious Adverse Events (SAE's):

The rates of SAE's similar between the active comparators. There were three serious gastrointestinal complications: one lower GI bleeding in the nabumetone group and two cases of cholecystitis, one in each active treatment group. There were no PUB's.

There were six cases of serious cardiovascular events in the rofecoxib group (4 MI and 2 CVA's); three in the nabumetone group (1 MI, 1 coronary artery disease and 1 CHF) and one coronary artery occlusion in the placebo group.

3. Discontinuations due to AE's

The incidence of discontinuations due to clinical and laboratory AE's were similar. Discontinuations by body system are presented in the following table.

Table 10. Discontinuations due to clinical AEs in study 085 and 090

	Rofecoxib 12.5 mg (N=814)	Nabumetone 1000 mg (N=802)	Placebo (N=404)
	n (%)	n (%)	n (%)
Body As A Whole/Site Unspecified	13 (1.6)	11 (1.4)	4 (1)
Cardiovascular System	10 (1.2)	3 (0.4)	1 (0.2)
Digestive System	19 (2.3)	18 (2.2)	0
Musculoskeletal System	5 (0.6)	9 (1.1)	3 (0.7)
Nervous System	6 (0.7)	4 (0.5)	0
Respiratory System	2 (0.2)	2 (0.2)	1 (0.2)
Skin And Skin Appendages	6 (0.7)	2 (0.2)	3 (0.7)
Urogenital System	0	1 (0.2)	1 (0.2)

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.

Discontinuations in the Digestive system were similar in both active groups and higher than placebo. Discontinuations in the CV system were twice in the rofecoxib 12.5 mg dose than in nabumetone 1000 mg dose.

4. Laboratory AE's

Two patients in the rofecoxib 25 mg group, one in the nabumetone 1000 mg group and one patient on placebo discontinued due to laboratory AE's

> *Population size, dose and duration limit the value of these studies in assessing the safety of chronic rofecoxib use. However, there were 6 cardiovascular thrombotic events in the rofecoxib group and two in the nabumetone group. The number of events is small to allow statistical comparisons but results appear to follow the pattern observed in the VIGOR study for CV thrombotic events.*

2.1.3 Study 102

Study 102 ("ADVANTAGE") was a 12-week, randomized, double blind active controlled study of rofecoxib 25 mg/day and naproxen 1000 mg/day in approximately 5500 patients with OA who were allowed low dose ASA (81 to 325 mg/day). Patients taking low dose ASA were 12.1% and 12.8% in the rofecoxib and naproxen treatment group, respectively.

> *This study was completed in March 2000. Unfortunately this large database was not included with this supplement submission. The short duration of the study is*

noted. At the FDA request, preliminary data on GI and CV events were submitted in 12/21/00. Baseline demographics by treatment arm have not been provided.

a. Serious GI: Preliminary Results

There were 6 clinical upper GI events in the rofecoxib 25 mg group and 12 in the naproxen 1000 mg group.

The small number of serious GI events and the relatively short duration of treatment do not allow statistical comparisons. However, there is a trend in favor of rofecoxib

b. Serious CV events: Preliminary results.

There were 6 myocardial infarctions (MI) in the rofecoxib 25 mg group and one MI in the naproxen 1000 mg group. Of the 6 MI in the rofecoxib group, 3 were in patients taking low ASA for cardiovascular prophylaxis. The patient with MI in the naproxen group was a non-ASA user.

A trend towards an excess of MI's in the rofecoxib 25 mg group in a 12 week study is noted. This observation is consistent with the pattern seen in VIGOR.

2. 2 Data from the original NDA.

In addition to the new studies, this supplement refers to study 058 and 069 from the original NDA.

Study 058 was a double-blind, randomized, placebo-controlled, 6-week study of rofecoxib 12.5 and 25 mg/day and nabumetone 1000 mg/day in elderly patients with OA. Seventy percent of patients were taking prophylactic ASA.

> *Because of the small size and short duration, this study is inadequate to detect differences in clinically relevant adverse events between rofecoxib and nabumetone.*

Study 069 was a pooled analysis of gastrointestinal events from all OA studies conducted under the original NDA. The analysis compared PUB's between rofecoxib – pooled doses, despite the evidence of dose-related adverse events – and other NSAIDs (pooled data from ibuprofen 2400 mg/day, diclofenac 150 mg/day and nabumetone 1000 mg/day, each one with different risk of GI bleeding). These studies were of different duration (from 6 weeks to 86 months). Most patients were exposed for less than 6 months.

> *The Division has serious concerns with a combined analysis of studies of different length and dosing regimens. Furthermore, combining multiple different drugs within a single comparator arm may not be reflective of the risk of any one drug. These concerns were discussed extensively during the Advisory Committee Meeting of April 20, 1999.*

Similarly, the sponsor conducted a meta-analysis of CV thrombotic events in the OA database.

> *This database overall included short term, low doses of rofecoxib. Most of the exposure for more than 6 months was at the 12.5 and 25 mg QD doses. Two hundred and seventy two patients received 50 mg QD for z 6 months (265 in OA trials); the rest of the exposure to z50 mg was in short-term studies. The Division has requested a meta-analysis based on dose and duration.*
>
> *None of the studies were powered to detect differences in serious CV thrombotic events compared to the active comparator, but more important, the studies involved a different population.*
>
> *Patients with RA have been recently reported to have twice the risk of cardiovascular events compared with OA. There is increasing evidence that ongoing inflammation is a risk factor for coronary disease (plaque unstability). It is likely that the RA population is a very sensitive model for detecting differences in the beneficial or deleterious effects of any drug on cardiovascular risk.*

2.3 Post-marketing data

From May 1999 to October 25, 2000, thirty-seven deaths after experiencing GI bleeding, perforation or obstruction have been reported to the FDA AERS system in association with the use of rofecoxib.

Table 11. Summary of deaths due to GI complications reported to FDA AERS in association with the use of rofecoxib (May 1999 to October 1999).

Age in years	Mean 76, median 80, range 28 to 93
Gender	Male (14), Female (22), Unknown (1)
Year	1999 (3), 2000 (34)
Indication	Osteoarthritis (14), Acute pain (6), Unspecified arthritis (6), Other (6), Unknown (5)
Time to onset	Mean 43, median 21 (range, 0 to 131) days
Dose	At or below labeled range (24), Higher than labeled range (1), Unknown (12)
GI event	Hemorrhage (23), Perforation (7), Melena (4), Hematemesis (6), Erosions (1), Stenosis/Obstruction (1), Other (10)
Location	Gastric (13), Duodenal (5), Large intestine (2), Other (2), Unknown (15)
Pertinent PMH	Anemia (1), ASA allergy (1), sulfa allergy (1), Crohn's disease (1), CVA (1), Diabetes (1), Diverticulitis (1), Functional intestinal disorder (1), Gastrostomy (1), Previous GI bleed (1), Irritable bowel syndrome (1), Hepatic dysfunction (1), PUD (4)
Major event preceding bleed	Metastatic gastric cancer (1), Pancreatitis, hepatitis (1), Shock (1) Surgery (3)
Significant concomitant meds.	ASA (8), Clopidogril (2), Corticosteroid (2), Warfarin (6) Antacid, H2 blocker, or PPI (4)

Source: Joyce Weaver, Pharm.D., Safety Evaluator. Office of Post-marketing Drug Risk Assessment.

Inherent limitations to the spontaneous report system are the lack of known denominator (number of patients at risk), the under-reporting of events and the multiple confounding variables. Despite these limitations, post marketing surveillance does inform in the evaluation of the safety profile of a drug.

The risk of serious gastrointestinal complications with rofecoxib is still a concern. Risk factors associated with serious gastrointestinal bleeding with rofecoxib are the same as for other NSAIDS: age, prior history of ulcer disease, concomitant use of ASA, warfarin or antiplatelet agents and corticosteroids.

Other NSAID class related adverse events such as anaphylactoid reactions, interstitial nephritis, papillary necrosis and clinically significant drug interactions with coumadin were reported within a few months of post-marketing surveillance. An analysis of post-marketing CV thrombotic events is currently being conducted.

3. Conclusions

1. The sponsor has demonstrated a statistically significant reduction associated with the use of rofecoxib compared to naproxen in PUBs and complicated PUB's, in this population of patients not taking low dose ASA. The cumulative incidence of PUB's was 2.08% and 4.49% for rofecoxib and naproxen, respectively. The cumulative incidence of **complicated** PUB's was 0.59% and 1.37% in the rofecoxib and naproxen groups, respectively. The cumulative risk of PUB's in both groups is similar to the rate range for one year that appears in the current GI warning section of NSAID labels (2 to 4%).

2. This risk reduction in relevant GI events did not translate into an overall safety benefit of rofecoxib over naproxen. GI safety must be assessed within the overall safety profile of a drug. Evaluation of safety by routine parameters showed no advantage of rofecoxib over naproxen:

	Rofecoxib 50 mg N=4047 (%)	Naproxen 1000 mg N=4029 (%)
a. Deaths	22 (0.5)	15 (0.4)
b. Serious AEs	378 (9.3)	315 (7.8)
c. Dropouts due to AEs	643 (15.9)	635 (15.8)
d. Serious lab AEs	2 (0)	0 (0)
e. Dropouts due to lab AEs	22 (0.5)	12 (0.3)

Other than GI and CV, the safety profile of rofecoxib and naproxen showed a similar pattern and was consistent with that of the NSAID class. NSAID-related (liver, renal, HTN and edema-related AE's) were consistently higher in the rofecoxib group.

3. The relative risk of cardiovascular thrombotic events was twice in rofecoxib compared with naproxen. Cumulative risk was 1.67% and 0.7% for rofecoxib and naproxen, respectively (mainly due to the higher risk of MI). In addition to CV thrombotic events, rofecoxib had a higher incidence of discontinuations due to HTN- and CHF related events compared with naproxen. These differences were statistically significant.

   Safety profiles must be carefully analyzed based on events of comparable severity and seriousness. In the VIGOR study the potential advantage of decreasing the risk of complicated PUB's was paralleled by the increased risk of developing cardiovascular thrombotic events.

4. The sponsor recommends that patients with known cardiovascular risk should be on prophylactic ASA, however, outstanding issues are:

   a. Whether any of the cardiovascular effects potentially associated with rofecoxib will be prevented by ASA

b. Whether the addition of ASA will decrease or abolish the GI advantage of rofecoxib over naproxen.

There are no data available to answer these questions. The sponsor proposes that studies 085, 090 and 058 support the safety of the concomitant use of rofecoxib and ASA. Each of these three studies was designed as an efficacy trial and neither the size nor the duration was adequate to detect differences in serious gastrointestinal events. The doses of rofecoxib used in these studies were one fourth and one half of the dose used in the VIGOR study.

Study 102 compared rofecoxib (25 mg/day) and naproxen (1000 mg/day) for 12 weeks and allowed the use of low dose ASA. Preliminary results of GI clinical events in this study showed a trend in favor of rofecoxib. However, it also showed a pattern of myocardial infarctions consistent with the VIGOR study.

5. Despite a substantial risk reduction compared to naproxen in the VIGOR study, the risk of serious GI complications with rofecoxib is still a concern. From May 1999 to October 2000, the FDA post-marketing AER system received 37 unduplicated reports of death due to gastrointestinal complications associated with the use of rofecoxib. Risk factors associated with serious GI complications are similar to those associated with conventional NSAIDs: age, prior history of ulcer disease, concomitant use of ASA, coumadin or other antiplatelet agents, and corticosteroids.

4. Recommendations

1. The NSAID-class GI warning should not be removed from the VIOXX label.

2. Information regarding cardiovascular thrombotic events should be added to the VIOXX label.

3. Additional studies may be needed to optimally clarify outstanding questions.

_____
Maria Lourdes Villalba, M.D.,
Medical Officer, DAAODP

_____
Lawrence Goldkind, M.D.,
Team Leader, DAAODP

Appendix 1. VIGOR. Deaths in patients treated with Rofecoxib 50 mg.

ID/ Study	Age/ Gender	Rel[1] (days)	Serious adverse event	Other RA meds	Medical history
324/088	69 F	174	Ventricular fibrillation/sudden death	MTX	HTN
229/088	70 F	132	Adult respiratory distress syndrome	MTX, HCQ, Pred	HTN, pulm fibrosis
731/088	77 F	254	Pneumonia	MTX	Pulmonary fibrosis
2560/088	78 M	41	Penetrating duodenal ulcer, pneumonia, septic shock.	MTX	GI bleeding, COPD
2662/088	62 F	26	Perforating hemorrhagic gastric ulcer, subphrenic abcess, septic shock.*	Gold, Prednisone	COPD, smoker
1224/088	68 F	46	Myocardial infarction, multiple organ failure.	Gold, Predinsone	Smoker, gout
920/088	68 F	205	Cerebrovascular accident; complete heart block.	MTX, Prednisone	HTN, ⎫chol, GI ulcer
2759/088	69 M	94	Myocardial infarction.		⎫chol, family hx CAD
5687/089	53 M	283	Gastric neoplasm.	MTX, Pred, CQ	
7285/089	71 M	69	Pneumonia.	MTX, Prednisone	
8104/089	57 M	101	Gastrointestinal bleeding.	Prednisone	
5305/089	75 F	309	Cardiac arrest. Sudden death.	MTX, Prednisone	HTN, CAD, pulm fibr.
5316/089	80 M	90	Interstitial lung disease.	MTX, CQ, Pred	Pulm fibr., gastritis
8021/089	84 F	302	Hip fracture, pneumonia, respiratory failure	MTX, Prednisone	HTN, Pulm fibr., MI
7620/089	55 F	31	Dissecting aortic aneurism	MTX, Pred, CQ	HTN, MI, dyspepsia
5591/089	51 F	206	Cerebrovascular accident.	Prednisone, CQ	HTN
6103/089	65 F	340	Worsening rheumatoid arthritis (lung).	Prednisone, HCQ	Interst pneumonitis
7461/089	56 F	25	Pulmonary infection. Bacterial sepsis.	MTX	HTN, gammopathy
7973/089	71 M	147	Myocardial infarction.	MTX	Asthma
7553/089	51 F	28	CHF? Unknown cause of death.		
10078/089	54 F	133	Aplastic anemia. Pneumonia. Sepsis.	MTX, Prednisone	
7689/089	60 F	206	Sudden death. **	MTX, Prednisone	HTN, DM

Source Table 54 of 088c study report; medical reviewer's review of narratives and CRFs. * Cause of death listed as pneumonia but patient died as a septic complication after GI surgery. ** Cause of death listed as Aortic Valve Stenosis but there is no documentation of A.S. in the autopsy.

Appendix 1. cont. NDA 21-042/s007. VIGOR. Deaths in patients treated with Naproxen 1000 mg.

ID/ Study	Age/ Gender	Rel[1] (days)	Serious adverse event	Other RA meds	Medical history
923/088	60 M	164	Cerebrovascular accident; myocardial infarction?; aortic thrombosis.		HTN, CAD, smoker, GI ulcer, prior carotid sx.
815/088	72 M	133	Metastatic neoplasm of unknown primary	MTX, HCQ, Pred	HTN, lymphoma
3097/088	78 F	9-29	Perforating gastric ulcer, septic shock.	MTX, Prednisone	HTN, dyspepsia, COPD
981/088	66 F	12-28	Respiratory failure. Pneumonitis. RA lung.		
2632/088	70 F	17	Sudden death**	MTX, Prednisone	HTN, MI, DM, ⎫chol
2229/088	79 F	247	Cerebrovascular accident. Intracraneal hemorrage.		HTN, renal insuff.
7732/089	62 M	61	Unknown cause of death/ sudden death**.	CQ, Prednisone	
7769/089	58 M	266	Sudden death.**		HTN, Atrial fibrillatio
10100/089	58 F	253	Pneumonia.	MTX, Pred, CQ	Gastritis
5590/089	55 F	215	Pneumonia. Electrolyte imbalance.	MTX, Pred, CQ	HTN, DM, dyspepsia
9191/089	62 F	260	Hepatic necrosis.	MTX[1], APAP, CQ	
6030/089	51 M	44-106	Lung malignant neoplasm.	AZA, Pred, SSZ	
6057/089	60 M	200	Sudden death.**	MTX	HTN, gout
6703/089	53 F	205	Intracranial hemorrhage	MTX, Prednisone	
6912/089	76 F	52	Pneumonia.	MTX, HCQ, Pred	Gastric ulcer, depression

Source Table 54 of 088c study report; medical reviewer's review of narratives and CRFs. ** Cause of death listed as myocardial infarction but there were no documented MI in the CRF. [1] MTX three times a week.

Appendix 2.a. Adjudicated Thrombotic Cardiovascular Serious Adverse Experiences in VIGOR (updated application data) (Source: sponsor's table)

Event	Rofecoxib (N=4047)		Naproxen (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.

Appendix 2.b. Summary of Analysis of Confirmed Adjudicated Thrombotic Cardiovascular Serious Adverse Experiences in VIGOR study. (Source: sponsor's Table 5, updated application data).

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.