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

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

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

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

† Patient-years at risk.
‡ Per 100 PYR.
§ Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.
% Includes sudden death, unknown cause of death, fatal myocardial infarction, fatal stroke (hemorrhagic or ischemic), fatal subarachnoid hemorrhage, fatal primary intracranial hemorrhage, fatal gastrointestinal bleeding episode.
¶ Includes fatal and nonfatal ischemic strokes, and fatal or nonfatal hemorrhagic strokes.
§ Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.
% Includes sudden death, unknown cause of death, fatal myocardial infarction, fatal stroke (hemorrhagic or ischemic), fatal subarachnoid hemorrhage, fatal primary intracranial hemorrhage, fatal GI bleeding episode.
¶ Includes fatal or nonfatal ischemic strokes, and fatal or nonfatal hemorrhagic strokes.
# "Aspirin Indicated" patients are patients with past medical histories of cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, angina pectoris, coronary artery bypass graft surgery, or percutaneous coronary interventions). [84] "Aspirin Not Indicated" patients are patients without a past medical history of these conditions.
[Attachment 3]

Serious Cardiovascular Adverse Experiences

The following table was sent in a 10/13/00 safety update and represents confirmed adjudicated cardiovascular serious adverse experiences, as presented by the sponsor.
Of the breakdown of thrombotic events, it is the cardiac events which are significantly different (i.e., the Confidence Interval does not cross 1.0). It should be noted that the other categories have a smaller number of events but show consistently higher numbers of events, rates, and relative risk estimates in the rofecoxib group.

Summary of Analysis of Confirmed Adjudicated Thrombotic Cardiovascular Serious Adverse Experiences VIGOR Study in Patients With Rheumatoid Arthritis†
Updated Application
Data (10/13/00)

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

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

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

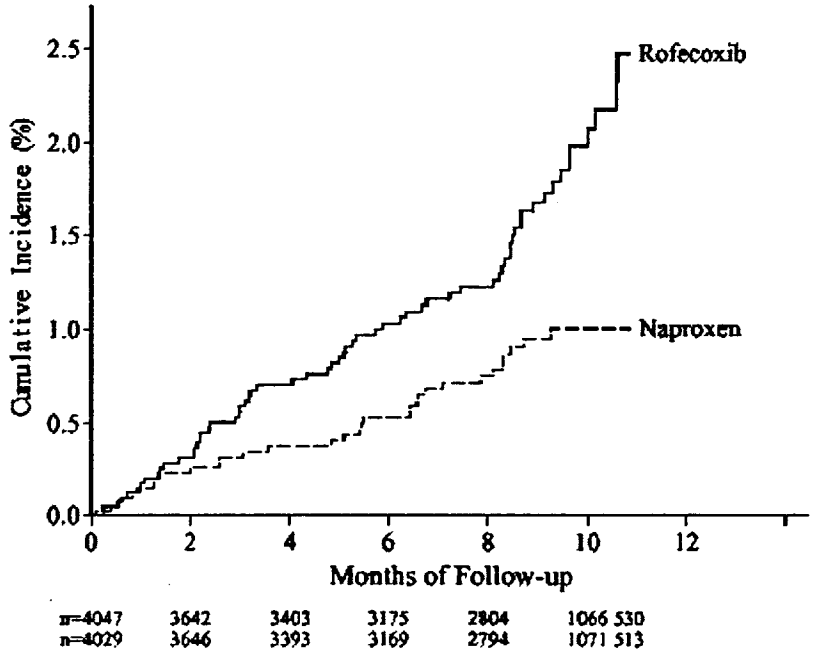
§ Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.

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

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

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)

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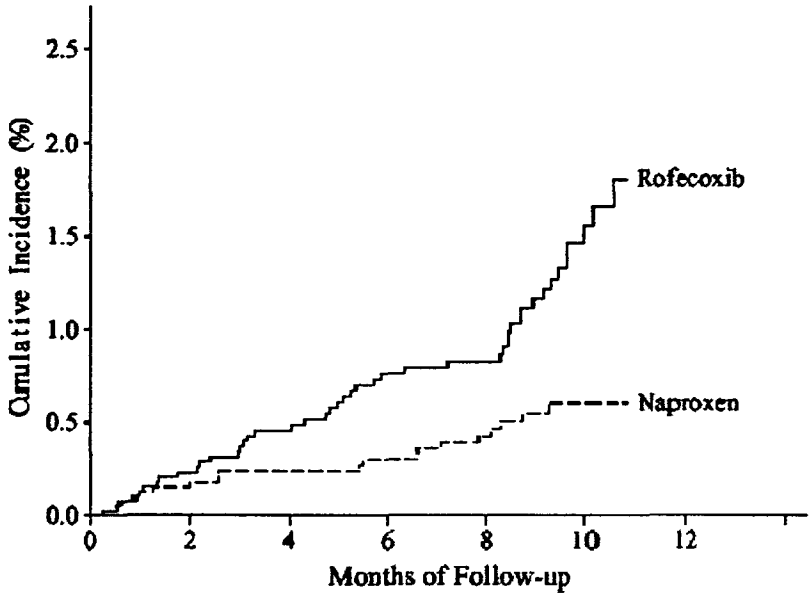
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
in Rheumatoid Arthritis Patients in the VIGOR Study
Time-to-Event Plot (All Patients Randomized)
Updated Application Data



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

Data Source: [P088C], [Attachment 3]

Adjudicated Thrombotic Serious Cardiovascular Adverse Experiences–Specific Events

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

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

Deaths:

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

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

Deaths: Rofecoxib group: Medical Reviewer's analysis

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

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

Deaths: Rofecoxib group (cont.)

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

*This patient, coded as "congestive heart failure" in Table 55, presented to the ER with dyspnea and cyanosis, was given aminophylline and subsequently died; the cause of death was registered as "cardiac insufficiency" and no other details (EKG, labs) are given in the narrative. There is no history of asthma in the case report form; screening cardiac/pulmonary exam was normal. See sNDA S-007: CSR 088c: pdf page 1292.

‡This patient was coded in Table 55 as "aortic stenosis." According to the narrative, this patient with hypertension and diabetes died suddenly at home. Autopsy showed cardiac hypertrophy and pulmonary congestion; no finding of aortic valve abnormalities or asymmetric septal hypertrophy were reported. In the case report form, there is notation of "idiopathic hypertrophic subaortic stenosis;" the screening cardiac exam was noted as normal and the patient was on enalapril. No autopsy or echocardiographic findings are reported. Therefore, the Medical Reviewer reclassified this event as sudden death. See sNDA S-007: CSR 088c: pdf page 1293 for further details.

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

Deaths: Naproxen Group: Medical Reviewer's Analysis

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

The Reviewer has marked in bold those events possibly related to thrombosis/ischemia.

*Coded in Table 55 as myocardial infarction; however, this was sudden death according to the narrative.

** Coded in Table 55 as Unknown cause of death; according to the narrative, this patient was found dead in his home. The only additional information is a complaint of cough and chest pain the day before his demise.

°Coded as myocardial infarction; however, there is no documentation for myocardial infarction in the case report form. These patients were not hospitalized and are listed as deaths.

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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:

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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	
Subgroup	Treatment Group	N	n	(%)
Incidence of an Edema-Related Adverse Experience				
Patients with a confirmed thrombotic cardiovascular serious adverse experience	Rofecoxib	45	1	(2.2)
Patients without a confirmed thrombotic cardiovascular serious adverse experience	Rofecoxib	4002	219	(5.5)
Patients with a confirmed thrombotic cardiovascular serious adverse experience	Naproxen	19	1	(5.3)
Patients without a confirmed thrombotic cardiovascular serious adverse experience	Naproxen	4010	144	(3.6)
Data Source: [P088C], [Attachment 3]				

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

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

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

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

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

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

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

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

Comments:

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

Study 085:

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

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

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

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

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

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

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

Results:

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

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

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

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

Adapted from: 085: pdf. page 817

Safety:

There were no deaths in this study.

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

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

Clinical Adverse Experience Summary

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

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

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

Note: This table presents counts of patients. Patients are counted only once per category but may be counted in more than 1 category.
Data Source: [4.1.41; 4.12]
(sNDA: 085 clinical study report: Table 34, pdf. page 102)

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

Rofecoxib

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

Nabumetone

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

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

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

Summary of Renal/Vascular Effects†

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

† Based on edema-related and hypertensive adverse experiences.
Note: This table presents counts of patients. Patients are counted only once per category (in bold-faced type) but may be counted in more than 1 category.
(Source: 085: pdf. page 117)

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

Clinical Adverse Experience Summary by Aspirin Subgroup

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

Data Source: [4.1.58; 4.1.59]

Comments:

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

Study 090:

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

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

Secondary Objectives:
As with study 085, the secondary objectives were superiority of rofecoxib to nabumetone and efficacy of both drugs to placebo, using assessment instruments of response to therapy.
in the percent of patients with good or excellent response to therapy, as

Study design:
This was a double-blind, parallel-group, placebo-controlled study comparing efficacy and safety of rofecoxib versus nabumetone after 6 weeks of treatment for osteoarthritis of the knee. Following a screening period, eligible patients were randomized to either rofecoxib 12.5 mg daily, nabumetone 1000 mg daily, or placebo for 6 weeks.

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

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

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

Results:

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

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

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

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

Baseline Patient Demographic Characteristics by Treatment Group

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

Data Source: [4.1.3; 4.2]

(Source: 090: pdf. Page 56)

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

Safety:

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

Clinical Adverse Experience Summary

Number (%) of patients:	n	Rofecoxib 12.5 mg (N=390) (%)	n	Nabumetone 1000 mg (N=392) (%)	n	Placebo (N=196) (%)	n	Total (N=978) (%)
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.

* $p \leq 0.05$ versus placebo.

** $p \leq 0.05$ 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

	n	Rofecoxib 12.5 mg (N=390) (%)	n	Nabumetone 1000 mg (N=392) (%)	n	Placebo (N=196) (%)	n	Total (N=978) (%)
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

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Summary of Renal/Vascular Adverse Experiences†

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

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

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

Clinical Adverse Experience Summary by Aspirin Subgroup

Clinical Adverse Experiences	Rofecoxib 12.5 mg (N=390) Low dose aspirin (N=45) n	%	Non-user (N=345) n	%	Nabumetone 1000 mg (N=392) Low dose aspirin (N=47) n	%	Non-user (N=345) n	%	Placebo (N=196) Low dose aspirin (N=27) n	%	Non-user (N=169) 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)

Adapted from 090: Table 44: page 133

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:

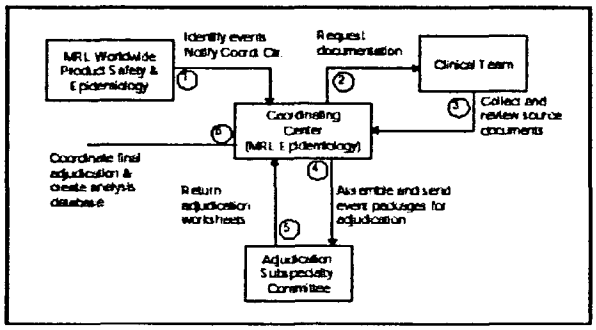
Specific issues requested by the Division:

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). It should be noted that the DSMB was relieved to learn of the "cardioprotective effect of Treatment B" while reviewing the safety analysis (it appears to this Medical Reviewer that the DSMB was influenced by the sponsor toward this conclusion).

Figure C-1

Overview of Cardiovascular Event Surveillance, Monitoring, and Adjudication



2. Evaluation of CV events in other rofecoxib studies that allowed ASA (085 and 090):

See Comments on 085 and 090. Despite lower dose, smaller sample size and aspirin use, the trend is against rofecoxib.

3. Assessment of CV thrombotic risks in this database:

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

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

<u>The sponsor's claims:</u>

- <u>The sponsor claims that the difference in myocardial infarctions between the two groups is primarily due to the antiplatelet effects of naproxen.</u> This hypothesis is not supported by any prospective placebo-controlled trials with naproxen. One can further argue that, no matter what the attribution, the results (from a cardiovascular standpoint) are favorable for naproxen.

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

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

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

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

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

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

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

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

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

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

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

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

RECOMMENDATIONS:

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

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

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ON ORIGINAL

/s/

Shari Targum
1/4/01 12:07:06 PM
MEDICAL OFFICER

Norman Stockbridge
1/5/01 06:57:59 AM
MEDICAL OFFICER

Raymond Lipicky
1/9/01 10:16:07 AM
MEDICAL OFFICER

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ON ORIGINAL

Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20816
Tel (301) 594-5384, FAX (301) 594-5494

Memorandum

DATE: February 3, 2001

FROM: Shari L. Targum, M.D., Medical Officer /S/
Division of Cardio-Renal Drug Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Team Leader /S/ 2/5/01
Division of Cardio-Renal Drug Products, HFD-110
Raymond Lipicky, M.D., Director
Division of Cardio-Renal Drug Products, HFD-110

TO: Sandra Folkendt, 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 drug effects on renal safety.

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. NDA 21-042: Prior Consultation from HFD-110 on cardiovascular safety (Dr. Targum), 12/8/2000
3. NDA 21-042 (rofecoxib): Prior Consultation from HFD-110 on renal safety (Dr. Pelayo), 4/30/99;
4. NDA 21-042/21-052 (rofecoxib): Primary Medical Review (Dr. Villalba), 5/20/99

DATE CONSULT RECEIVED: 12.11.2000
DATE CONSULT COMPLETED: 2.3.2001

The Division of Ophthalmic and Anti-Inflammatory Drug Products (HFD-550) has requested a review of renal safety in the VIGOR trial. A review of cardiovascular safety events for VIGOR has been recently completed by this Medical Reviewer.

Background:

Cox-2 inhibitors and rofecoxib:

For a background on rofecoxib and Cox-2 inhibitors, please see the prior consultation on cardiovascular safety (Shari L. Targum, M.D., 12/8/2000).

Prior renal safety review:

In the original NDA for osteoarthritis, a review from HFD-110 (Juan Carlos Pelayo, M.D.) concluded the following:

1. There was a dose-dependent increase in hypertension, edema, increased serum creatinine, hyperkalemia, and, to a lesser extent, proteinuria.
2. The vascular-renal safety profile of rofecoxib was distinguishable from placebo and qualitatively similar to other NSAIDs; it appeared, however, that these adverse events occurred at a higher rate with rofecoxib 50 mg than with other NSAIDs at their recommended dosage.

Current Rofecoxib Labeling (Renal Safety):

The current labeling for VIOXX™ contains the following renal safety information:

Under WARNINGS:

Advanced Renal Disease

No safety information is available regarding the use of VIOXX in patients with advanced kidney disease. Therefore, treatment with VIOXX is not recommended in these patients. If VIOXX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS , *Renal Effects*).

Under PRECAUTIONS:

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with VIOXX at daily doses of 12.5 and 25 mg have shown renal effects (e.g., hypertension, edema) similar to those observed with comparator NSAIDs; these occur with an increased frequency with chronic use of VIOXX at doses above the 12.5 to 25 mg range. (See ADVERSE REACTIONS .)

Caution should be used when initiating treatment with VIOXX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with VIOXX. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS , *Advanced Renal Disease*).

Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking VIOXX (see ADVERSE REACTIONS). VIOXX should be used with caution, and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or heart failure.

ADVERSE REACTIONS

In the OA studies, the following spontaneous adverse events occurred in >0.1% to 1.9% of patients treated with VIOXX regardless of causality:

Urogenital System: acute renal failure, breast malignant neoplasm, *interstitial nephritis,* prostatic malignant neoplasm, urolithiasis, *worsening chronic renal failure.*

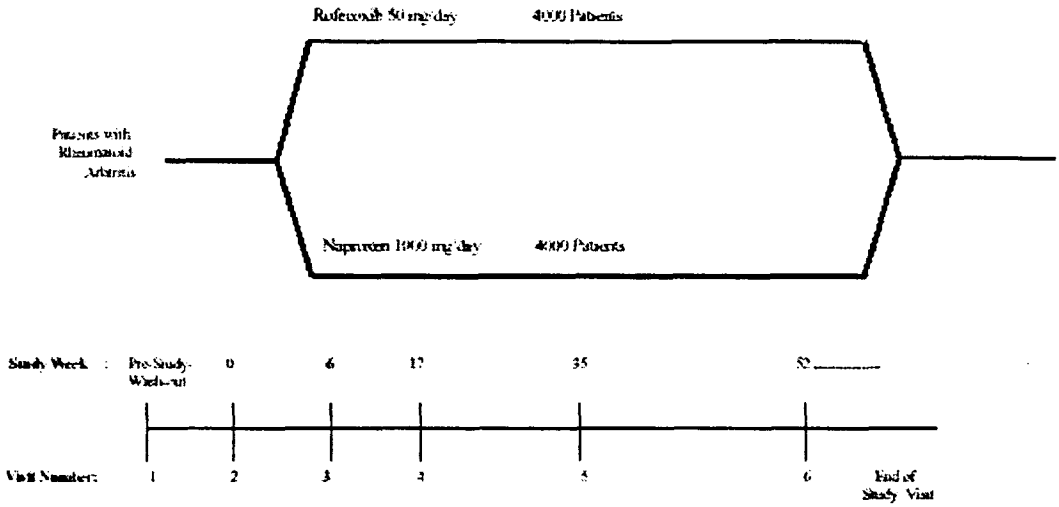
Review of Database from VIGOR:

Study Design:

The Study Design is summarized below (Source: 21-042, S-007 Figure 1 pdf. Page 48)

Figure 1

Study Design



Protocol, Demographics and Methods: The reader is referred to the Primary Medical Review (Maria L. Villalba, M.D.) and the HFD-110 consultation of cardiovascular safety (Shari L. Targum, M.D., 12/8/2000) for a discussion of the protocol, baseline characteristics and drug exposure in the VIGOR study.

Data Collection:

Physical exam: Vital signs, including blood pressure, and weights were done at all scheduled visits.
Laboratory tests: Serum chemistry was done at Visits 1 (prestudy), 3 (Week 6), 6 (Week 52), end of study, and at the discontinuation visit. A urinalysis was obtained at Visits 1, 3, end of study, and at the discontinuation visit.

Definitions of Limits of Change from Baseline: (Source: 21-042, S-007, Table 8, pdf. Page 64)

Creatinine (mg/dL) : Consecutive values with absolute increase >0.5 mg/dL and > ULN -OR- 1 value with increase ≥0.5 mg/dL and > ULN associated with discontinuation of study drug.

Potassium (mEq/L) : Consecutive values with absolute decrease ≥0.8 and <LLN -OR- 1 such value associated with a discontinuation study drug. Consecutive values with absolute increase ≥0.8 and >ULN -OR- 1 such value > ULN associated with a discontinuation study drug.

Calcium (mg/dL): Absolute increase ≥1.5 and >ULN
Absolute decrease ≥1.5 and <LLN

Sodium (mEq/L): Absolute decrease ≥8 and <LLN
Absolute increase ≥8 and >ULN

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Safety Results:

Renal Adverse Experiences:

Clinical Adverse Experiences:

NUMBER (%) OF PATIENTS WITH SPECIFIC CLINICAL ADVERSE EXPERIENCES (INCIDENCE >=0% IN ONE OR MORE TREATMENT GROUPS) BY BODY SYSTEM

Adverse Experience	**Rofecoxib** (N=4047) n(%)	**Naproxen** (N=4029) n (%)
Renal Failure*	2 (0.0)	2 (0.0)
Renal Insufficiency	3 (0.1)	1 (0.0)
Interstitial Nephritis	0 (0.0)	1 (0.0)
Glomerulonephritis	1 (0.0)	0 (0.0)
Urolithiasis	**15 (0.4)**	**7 (0.2)**
Hematuria	10 (0.2)	7 (0.2)
Dysuria	10 (0.2)	8 (0.2)
Urinary Tract Infection	172 (4.3)	187 (4.6)
Lower Urinary Tract Infection	5 (0.0)	0 (0.0)
Upper Urinary Tract Infection	0 (0.0)	2 (0.0)
Pyelonephritis	1 (0.0)	3 (0.1)
Urinary Tract Obstruction	1 (0.0)	1 (0.0)
Proteinuria	4 (0.1)	4 (0.1)
Nephrotic Syndrome	1 (0.0)	0 (0.0)

*Includes the terms: Renal Failure or Acute Renal Failure

Source: Appendix 4.17.1 pdf. Pages 3186-3210.

There appears to be an increased percentage of patients with urolithiasis in the rofecoxib group. This finding is already noted in the rofecoxib labeling (under adverse experiences in the OA studies). Otherwise there appear to be no meaningful differences between the two groups in the above table.

Laboratory Adverse Experiences:

NUMBER (%) OF PATIENTS WITH SPECIFIC LABORATORY ADVERSE EXPERIENCES BY LABORATORY TEST CATEGORY

Adverse Experience	**Rofecoxib** (N=4047) n/N(%)	**Naproxen** (N=4029) n/N (%)
Blood Chemistry:		
Blood Urea Nitrogen (BUN) Increased	**20/3989 (0.5)**	**9/3992 (0.2)**
Serum Creatinine Increased	**38/3988 (1.0)**	**27/3995 (0.7)**
Serum Creatinine Decreased	0/3988 (0.0)	1/3995 (0.0)
Hyperkalemia	4/3990 (0.1)	7/3992 (0.2)
Hypokalemia	3/3990 (0.1)	6/3992 (0.2)
Hyponatremia	6/3990 (0.2)	2/3991 (0.1)
Serum Albumin Decreased	3/3987 (0.1)	2/3991 (0.1)

Laboratory Adverse Experiences (cont.):

Adverse Experience	**Rofecoxib** (N=4047) n/N(%)	**Naproxen** (N=4029) n/N (%)
Urinalysis		
Proteinuria	17/3972 (0.4)	15/3973 (0.4)
Albuminuria	0/3972 (0.0)	3/3973 (0.1)
Leukocyturia	26/2021 (1.3)	18/1831 (1.0)
Erythrocyturia	**22/3972 (0.6)**	**5/3974 (0.1)**

Source: Appendix 4.18.1; pdf. Pages 3239-3242.

The number and percent of patients with increased BUN and serum creatinine are higher in the rofecoxib group compared with the naproxen group. This is consistent with the prior renal consultation for rofecoxib, which found a dose-dependent increase in renal/vascular events (including increased creatinine) as well as a higher rate of events with rofecoxib 50 mg daily compared with other NSAIDs. Also noted is a higher rate of erythrocyturia; it is possible that this finding is related to urolithiasis (otherwise the significance is unclear).

Discontinuations due to Renal-Related Clinical Adverse Experiences:

NUMBER (%) OF PATIENTS WITH SPECIFIC CLINICAL ADVERSE EXPERIENCES (INCIDENCE >=0% IN ONE OR MORE TREATMENT GROUPS) BY BODY SYSTEM **DISCONTINUED**

Adverse Experience	**Rofecoxib** (N=4047) N(%)	**Naproxen** (N=4029) n (%)
Hematuria	1 (0.0)	1 (0.0)
Nephrotic Syndrome	1 (0.0)	0 (0.0)
Proteinuria	0 (0.0)	2 (0.0)
Pyelonephritis	0 (0.0)	1 (0.0)
Renal Failure	0 (0.0)	1 (0.0)
Renal Insufficiency	0 (0.0)	1 (0.0)
Urolithiasis	1 (0.0)	1 (0.0)
Urinary Tract Infection	2 (0.0)	0 (0.0)

Source: 4.17.2: pdf. Pages 3211-3218

Discontinuations due to Laboratory Adverse Experiences:

NUMBER (%) OF PATIENTS WITH SPECIFIC LABORATORY ADVERSE EXPERIENCES BY LABORATORY TEST CATEGORY **DISCONTINUED**

Adverse Experience	**Rofecoxib** (N=4047) n/N(%)	**Naproxen** (N=4029) n/N (%)
Blood Chemistry:		
BUN Increased	2/3989 (0.1)	1/3992 (0.0)
Serum Creatinine Increased	7/3988 (0.2)	5/3995 (0.1)
Hyperkalemia	0/3990 (0.0)	1/3992 (0.0)

Source: 4.18.2. pdf. Page 3243

Serious Renal Adverse Events:

For a review of the narratives of serious renal adverse events please see Dr. Villalba's Review.
On the following page is a listing of serious renal adverse events. The event rate appears to be low and there do not appear to be meaningful differences between the two groups.

NUMBER (%) OF PATIENTS WITH SPECIFIC CLINICAL ADVERSE EXPERIENCES (INCIDENCE >=0% IN ONE OR MORE TREATMENT GROUPS) BY BODY SYSTEM **SERIOUS**		
	Rofecoxib	**Naproxen**
	(N=4047)	(N=4029)
Adverse Experience	n (%)	n (%)
Hematuria	0 (0.0)	1 (0.0)
Interstitial Nephritis	0 (0.0)	1 (0.0)
Nephrotic Syndrome	1 (0.0)	0 (0.0)
Proteinuria	0 (0.0)	1 (0.0)
Pyelonephritis	1 (0.0)	2 (0.0)
Renal Colic	1 (0.0)	1 (0.0)
Renal Disorder	0 (0.0)	1 (0.0)
Renal Failure*	1 (0.0)	2(0.0)
Renal Insufficiency	0 (0.0)	1 (0.0)
Urethral Obstruction	1 (0.0)	0 (0.0)
Urinary Tract Infection	5 (0.1)	3 (0.1)
Urolithiasis	2 (0.0)	1 (0.0)

(Source: 21-042: Appendix 4.17.4 pdf. Pages 3229-3237)
*Includes the terms: Renal Failure or Acute Renal Failure

Serious laboratory adverse experiences can be found in Appendix 4.18.4 (pdf. Page 3247). No renal serious laboratory adverse experiences are noted.

Renal Events--Deaths:

There were 37 deaths in this study: 22 in the rofecoxib group and 15 in the naproxen group.
In reviewing the patient narratives, the following 3 patients in the naproxen group had renal or electrolyte-related events:

- AN 3097, a 78 year old female in the naproxen group was reported as developing acute renal failure (requiring dialysis) following a perforated gastric ulcer, pneumonia, and adult respiratory distress syndrome (Source: 21-042, S-007: Table 55: pdf. Page 189).

- AN 5590, a 55 year old female in the naproxen group developed an electrolyte imbalance (unspecified) with pneumonia (Source: 21-042, S-007: Table 55: pdf. Page 190 Patient Narrative pdf. Page 3285).

- AN 9191, a 63 year old female in the naproxen group developed renal dysfunction in the setting of "massive hepatocellular necrosis" (on liver biopsy); her renal dysfunction was felt secondary to hepatorenal syndrome (Source: 21-042, S-007: patient narrative pdf. Page 3287).

Hypertension/Edema:

The increased rate of hypertension and edema in the rofecoxib group, compared with naproxen, can be noted in the following tables for Clinical Adverse Experiences, Serious Adverse Experiences, and Discontinuations due to Adverse Experiences.

Number (%) of Patients With Specific Clinical Adverse Experiences						
					Differences in Proportions	
	Rofecoxib		**Naproxen**		Rofecoxib	
	(N=4047)		(N=4029)		Minus	
	n	(%)	n	(%)	Naproxen	95% CI
Body As A Whole/Site Unspecified						
Edema	23	(0.6)	21	(0.5)	0.0	(-0.3, 0.4)
Lower Extremity Edema	161	(4.0)	104	(2.6)	1.4	(0.6, 2.2)
Upper Extremity Edema	16	(0.4)	8	(0.2)	0.2	(-0.1, 0.5)
Edema Peripheral	22	(0.5)	12	(0.3)	0.2	(-0.1, 0.6)
Fluid Retention	17	(0.4)	9	(0.2)	0.2	(-0.1, 0.5)
Total Edema	**239**	**(5.9)**	**154**	**(3.8)**	**2.1**	
Cardiovascular System						
Blood Pressure Increased	36	(0.9)	13	(0.3)	0.6	(0.20, 0.93)
Borderline Hypertension	2	(0.0)	2	(0.0)	0	(-0.1, 0.1)
Diastolic Hypertension	2	(0.0)	0	(0.0)	0	(-0.0, 0.1)
Hypertension	342	(8.5)	202	(5.0)	3.4	(2.32, 4.55)
Uncontrolled Hypertension*	8	(0.2)	5	(0.1)	0.1	--
Hypertensive Crisis	3	(0.1)	1	(0.0)	0.1	(-0.1, 0.2)
Total Hypertension	**393**	**(9.7)**	**223**	**(5.5)**	**4.2**	

*Two combined categories: Uncontrolled Hypertension and Hypertension Uncontrolled with Medication. (Source: 088c:Appendix 4.17.1)

Number (%) of Patients With Specific **Serious** Clinical Adverse Experiences by Body System				
	Rofecoxib		**Naproxen**	
	(N=4047)		(N=4029)	
	n	(%)	n	(%)
Lower Extremity Edema	3	(0.1)	0	(0.0)
Hypertension	9	(0.2)	0	(0.0)
Hypertensive Crisis	0	(0.0)	1	(0.0)

Source: Appendix 4.17.4

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Number (%) of Patients **Discontinued** Due to Specific Clinical Adverse Experiences by Body System Source: Appendix 4.17.2				
	Rofecoxib		**Naproxen**	
	(N=4047)		(N=4029)	
	n	(%)	n	(%)
Edema	2	(0.0)	1	(0.0)
Fluid Retention	1	(0.0)	2	(0.0)
Peripheral Edema	3	(0.1)	2	(0.0)
Lower Extremity Edema	19	(0.5)	8	(0.2)
Blood Pressure Increased	2	(0.0)	1	(0.0)
Labile Hypertension	1	(0.0)	0	(0.0)
Hypertensive Crisis	1	(0.0)	1	(0.0)
Hypertension	23	(0.6)	4	(0.1)

Figure 17

Diastolic Blood Pressure (mm Hg)
Mean Change Over Time
All-Patients-Randomized

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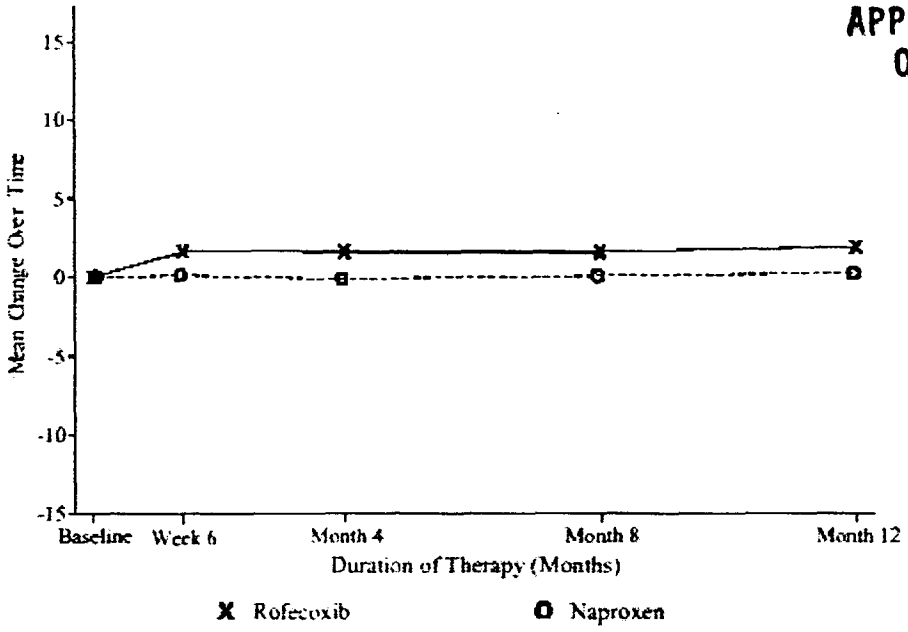

Other Laboratory Adverse Experiences:

There appears to be an increase in number and percent of patients with decrease in sodium in the rofecoxib group compared with naproxen. Alterations in sodium must be evaluated in the context of water balance. Since there appears to be an increased incidence of edema in the rofecoxib treatment group, it is more likely than not that this decrease in sodium is related to fluid retention/edema. There does not appear to be any meaningful difference in percent of patients with increased or decreased potassium.

Analysis of Laboratory Predefined Limits of Change Not Associated with Prespecified Adverse Experiences (Intention-to-Treat Approach)				
	Rofecoxib (N= 4047)	Naproxen (N= 4029)	Difference in Proportions	
Predefined Change	n(%)	n(%)	Estimate	95% CI
Sodium (mEq/L)				
• Absolute decrease ≥8 and <LLN	39 /3973 (1.0)	20 /3979 (0.5)	0.5	(0.1 , 0.9)
• Absolute increase ≥8 and >ULN	15 /3973 (0.4)	21 /3979 (0.5)	-0.2	(-0.5 , 0.2)
Potassium (mEq/L)				
• Consecutive values with absolute decrease ≥0.8 and <LLN or one such value associated with study drug discontinuation	1 /3973 (0.0)	0/3979 (0.0)	0.0	(-0.0 , 0.1)
• Consecutive values with absolute increase ≥0.8 and >ULN or one such value associated with study drug discontinuation	2 /3973 (0.1)	2/3979 (0.1)	0.0	(-0.1 , 0.1)
Calcium (mg/dL)				
• Absolute increase ≥1.5 and >ULN	1 /3966 (0.0)	8 /3978 (0.2)	-0.2	(-0.3 , -0.0)
• Absolute decrease ≥1.5 and <LLN	7 /3966 (0.2)	2 /3978 (0.1)	0.1	(-0.0 , 0.3)

Source: Appendix 4. 16.1: pdf. Page 3181

An analysis of those patients with a $\geq$ 25% increase from baseline of serum creatinine was requested from the sponsor. The following results were obtained:

Number (%) of Patients With Serum Creatinine Increase $\geq$ 25% Above Baseline

Laboratory Test	Rofecoxib (N=4047) n/m	(%)	Naproxen (N=4029) n/m	(%)
Serum Creatinine				
In patients with increase of >= 25%	1082/3970	(27.3)	856/3979	(21.5)
In patients with consecutive values with Increase of >= 25% or one or more values with increase >= 25% associated with study drug discontinuation	294/3970	(7.4)	208/3979	(5.2)

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ON ORIGINAL

CONCLUSIONS:

- **Edema:** There is an increased number and percentage of patients in the rofecoxib group with reports of edema compared with those in the naproxen group. This finding is consistent with the prior renal safety review.
- **Hypertension:** There is an increased number and percentage of patients in the rofecoxib group with reports of hypertension compared with those in the naproxen group. This finding is consistent with the prior renal safety review.
- **Creatinine increased:** A higher percentage of rofecoxib patients developed an increased serum creatinine compared with those on naproxen. This finding is consistent with the prior renal safety review.
- **BUN increased:** A higher percentage of rofecoxib patients developed an increased serum BUN compared with those on naproxen.
- **Hyper/hypokalemia and proteinuria:** The event rates of hyper/hypokalemia as well as proteinuria were low and not significantly different between the two groups.
- **Decreases in sodium**: There was an increase in numbers and percent of patients with decreases in sodium in the rofecoxib group compared with naproxen. This decrease in sodium is likely related to fluid retention (see Edema).
- The event rates for interstitial nephritis and renal failure were low in both treatment groups. No meaningful differences were seen in this regard.
- **Urolithiasis:** The increase in urolithiasis in the rofecoxib group is noted and already exists in the labeling.

[ ]

RECOMMENDATIONS:

The increased rate of edema, hypertension, and increased creatinine should be noted in the rofecoxib labeling.

Thank you.

CC: ORIG:
HFD-110/TARGUM
HFD-110/STOCKBRIDGE
HFD-110/LIPICKY
HFD-550/VILLALBA
HFD-550/GOLDKIND
HFD-550/FOLKENDT
HFD-550/BULL

APPEARS THIS WAY
ON ORIGINAL

VIOXX – NDA 21-042/s007
Memo to file

From: Maria Lourdes Villalba, M.D, M.O. DAAODP.
To: Lawrence Goldkind, M.D. Team Leader, DAAODP.

RE: Review of Safety Update
Date of submission: October 13, 2000.

The safety update for the VIGOR study included data on 11 additional patients who experienced cardiovascular serious adverse experiences eligible for adjudication. These additional events were included in the analyses and tables of serious cardiovascular adverse events in the main review.

/s/

Maria Villalba
4/4/01 02:24:18 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

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

Merck & Co., Inc.
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April 30, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

MERCK
Research Laboratories

Submitted through

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

Dear Dr. Bull

NDA 21-042: VIOXX™ (Rofecoxib Tablets)

Amendment to Supplemental New Drug Application
(Rheumatoid Arthritis)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on February 28, 2001, and a telephone conversation between Ms. Sandra Folkendt (FDA) and Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on April 25, 2001 regarding the Debarment Certification submitted on February 28, 2001.

As indicated on the attached Form FDA 356h, this amendment includes a revised copy of the Debarment Certification with an MRL signature.

All information is in electronic format as indicated in the Table of Contents for this amendment.

This amendment is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the amendment. All documents requiring signatures for certification are included as paper for archival purposes.

All the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of the CD are free of computer viruses (Norton AntiVirus® 4.0, Symantec Corp., 1991-1997) and we authorize the use of anti-virus software, as appropriate.

A list of Reviewers from the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products who should be provided access to this electronic submission from their desktops may be obtained from Ms. Sandra Folkendt, Project Manager.

We consider the filing of this amendment to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

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

Federal Express

Desk Copy: Ms. Sandra Folkendt, Project Manager
HFD- 550, Room N322

Q:\howley\christa\21042\FDA 4_30_01.doc

APPEARS THIS WAY
ON ORIGINAL

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

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Tel 610 397 2944
215 652 5000
Fax 610 397 2516

April 16, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products
Office of Drug Evaluation V

C/o

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

MERCK
Research Laboratories

Dear Dr. Bull:

NDA 21-042 / S-007 VIOXX™ (rofecoxib tablets)
Response to FDA Request for Information
(ADVANTAGE CSR – Item 11)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a fax dated February 14, 2001 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting the complete report for the ADVANTAGE study (Protocols 102 and 903); a FDA letter to MRL dated February 28, 2001 making an official request for the complete CSR for ADVANTAGE with the appropriate safety analysis similar to those ultimately performed for the VIGOR database; a letter from MRL to FDA dated March 15, 2001 containing our proposal for submission of the requested CSR; our submission dated March 30, 2001 containing the ADVANTAGE CSR without the associated elements of Items 11 and 12; an approvable letter dated April 6, 2001 which requested submission of Items 11 and 12; and a letter from MRL dated April 13, 2001 documenting MRL's intent to amend the sNDA with submission of Items 11 and 12.

By this letter, we are submitting Item 11 of the ADVANTAGE study. We are resubmitting the full CSR to include the appropriate links to Item 11. Item 12 will be submitted to the Agency by April 30, 2001.

This resubmitted CSR contains corrections to Tables 38 and 90 that were discovered after the CSR submission on March 30, 2001.

In conformance with the study protocol and established procedures, all gastrointestinal and cardiovascular clinical events reported by investigators in this study were adjudicated by independent committees. The documentation related to this process (Adjudication Packages) are provided in Item 20 of this submission.

All information is in an electronic format as indicated in the Table of Contents for this submission.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the amendment. All documents requiring signatures for certification are included as paper for archival purposes.

All the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of the CD are free of computer viruses (Norton AntiVirus® 4.0, Symantec Corp., 1991-1997) and we authorize the use of anti-virus software, as appropriate.

A list of Reviewers from the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products who should be provided access to this electronic submission from their desktops may be obtained from Ms. Sandra Folkendt, Project Manager.

We consider the filing of this amendment to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

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

Federal Express

Desk Copy Ms. Sandra Folkendt, Project Manager
HFD- 550, Room N322

Q:\ackd\vioxx\vigor\responses\ADVANTAGE CSR_covltr_Item11

APPEARS THIS WAY
ON ORIGINAL

STATEMENT OF ORGANIZATION

NDA 21-042 / S-007: VIOXX™ (rofecoxib tablets)

Response to FDA Request for Information (ADVANTAGE CSR – Item 11)

This supplemental New Drug Application contains the following paper and/or electronic information:

ITEM(s)	DESCRIPTION	Contents on Archival CD	Review Aids	Paper Review Copies
1	Administrative Documentation containing Archival CD*	Yes	No	Blue Binder (1 volume) Tan Binder (1 Volume) Green Binder (1 Volume)
8, 10	Clinical and Statistical Documentation	Yes	No	Tan Binder (1 Volume) Green Binder (1 Volume)
11	Case Report Tabulations	Yes (SAS Transport Files)	No	No

TOTAL VOLUMES: 5

* The Archival CD is provided in Volume 1 (Blue Binder).

APPEARS THIS WAY
ON ORIGINAL

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

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Tel 610 397 2944
215 652 5000
Fax 610 397 2516

April 5, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
Office of Drug Evaluation V

MERCK
Research Laboratories

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

Dear Dr. Bull:

NDA 21-042: VIOXX™ (Rofecoxib Tablets)
SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act and in accordance with 506A(d)(3)(B)(ii) of the Food and Drug Administration Modernization Act, we submit a supplement to NDA 21-042.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the *Labeling* Section of the approved New Drug Application for VIOXX™. The package circular has been revised to include post-marketing adverse reactions and post-marketing experience of hypersensitivity vasculitis and hyperkalemia. All information is in an electronic format as indicated in the Table of Contents for this supplemental application. The Statement of Organization following this letter describes the sections contained in this application.

The revised labeling will be used on or before November 1, 2001 in all packages sold or distributed from the Company's manufacturing facilities.

Attached on the CD, are the following items:

Labeling
I. Labeling history
II. Labeling text
  a. Proposed labeling text
    1. Package Circular (#9183807)
    2. Patient product information (#9183903)
  b. Currently used labeling text
    1. Package Circular (#9183806)
    2. Patient product information (#9183902)
  c. Last approved labeling text
    1. Package Circular (#9183804)
    2. Patient product information (#9183901)
III. Final printed package circular
    1. Package Circular (#9183807)
    2. Patient product information (#9183903)

APPEARS THIS WAY
ON ORIGINAL

Summary
I. Annotated package circular
  a. Package insert
  b. Patient product information

The Microsoft WORD version of the proposed labeling text is also provided on a separate diskette.

This supplemental application is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the supplemental application. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Sandra Folkendt, Regulatory Project Manager, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products.

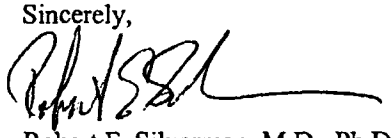
In accordance with the Prescription Drug User Fee Act of 1992 (PDUFA) and reauthorized in the Food and Drug Administration Modernization Act of 1997 (FDAMA), as indicated in the attached Form 3397, no user fee is required for this supplemental application.

Merck & Co., Inc. is requesting a categorical exclusion for the requirements to prepare an Environmental Assessment under 21 CFR 25.31(a). This supplement meets the requirements of a categorical exclusion under 21 CFR 25.31(a) because it will not increase the use of the active moiety. To the best of the firm's knowledge no extraordinary circumstances exist in regard to this action.

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Robert E. Silverman, M.D., Ph.D. (610-397-2944) or, in my absence, to Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,



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

Enclosure: CD

Federal Express #1

Desk Copies: (cover letter and diskette containing the WORD version of the proposed labeling)
Ms. Sandra Folkendt, Regulatory Project Manager
HFD-550, Rm. N322
Federal Express #2

Q:domingo/vioxx/labeling/AE CBE 042

STATEMENT OF ORGANIZATION

NDA 21-042: VIOXX™ (rofecoxib tablets)
SPECIAL SUPPLEMENT - CHANGES BEING AFFECTED

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

ITEM(s)	DESCRIPTION	Contents on Archival CD	Review Aids	Paper Review Copies
1, 16, 18, 19	Administrative Documentation containing Archival CD*	Yes	Yes (Word version of proposed labeling text**)	Blue Binder (1 volume)
2	Labeling			
3	Summary (Annotated Label)			

TOTAL VOLUMES: 1

* The Archival CD is provided in Volume 1 (Blue Binder).

** The diskette containing the WORD version of the proposed labeling text is being sent to the Project Manager.

APPEARS THIS WAY
ON ORIGINAL

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

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Tel 610 397 2944
215 652 5000
Fax 610 397 2516

March 30,2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products
Office of Drug Evaluation V

MERCK
Research Laboratories

C/o

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

Dear Dr. Bull:

NDA 21-042 / S-007 VIOXX™ (rofecoxib tablets)
Response to FDA Request for Information
(ADVANTAGE CSR)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a fax dated February 14, 2001 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting the complete report for the ADVANTAGE study (Protocols 102 and 903); a FDA letter to MRL dated February 28, 2001 making an official request for the complete CSR for ADVANTAGE with the appropriate safety analysis similar to those ultimately performed for the VIGOR database and a letter from MRL to FDA dated March 15, 2001 containing our proposal for submission of the requested CSR.

In the letter dated March 15, 2001, MRL promised to submit the requested CSR without the associated elements of Item 11 (e.g., SAS data sets) or Item 12 (e.g. copies of case report forms for patients who died or discontinued due to an adverse event) by March 30, 2001.

By this letter we are submitting the requested CSR for ADVANTAGE. Items 11 and 12 will be forthcoming if the Agency requires this information.

In conformance with the study protocol and established procedures, all gastrointestinal and cardiovascular clinical events reported by investigators in this study were adjudicated by independent committees. The documentation related to this process (Adjudication Packages) are provided in Item 20 of this submission.

All information is in an electronic format as indicated in the Table of Contents for this submission.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the amendment. All documents requiring signatures for certification are included as paper for archival purposes.

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A list of Reviewers from the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products who should be provided access to this electronic submission from their desktops may be obtained from Ms. Sandra Folkendt, Project Manager.

We consider the filing of this amendment to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

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

Federal Express

Desk Copy Ms. Sandra Folkendt, Project Manager
HFD- 550, Room N322

Q:\ackd\vioxx\vigor\responses\ADVANTAGE CSR_covltr

APPEARS THIS WAY
ON ORIGINAL

STATEMENT OF ORGANIZATION

NDA 21-042 / S-007: VIOXX™ (rofecoxib tablets)

Response to FDA Request for Information
(ADVANTAGE CSR)

This supplemental New Drug Application contains the following paper and/or electronic information:

ITEM(s)	DESCRIPTION	Contents on Archival CD	Review Aids	Paper Review Copies
1	Administrative Documentation containing Archival CD*	Yes	No	Blue Binder (1 volume) Tan Binder (1 Volume) Green Binder (1 Volume)
8, 10	Clinical and Statistical Documentation	Yes	No	Tan Binder (1 Volume) Green Binder (1 Volume)
20	Adjudication Packages	Yes	No	No

TOTAL VOLUMES: 5

* The Archival CD is provided in Volume 1 (Blue Binder).

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-042/S-007
NDA 21-052/S-004

INFORMATION REQUEST LETTER

Merck Research Laboratories
Attention: Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, Pennsylvania 19486

Dear Dr. Silverman:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vioxx (rofecoxib tablets) Tablets, 12. 5 mg, 25 mg, and 50 mg, and Vioxx (rofecoxib suspension) Suspension, 12.5 mg/5 mL and 25 mg/5 mL.

We are reviewing the Medical section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your supplemental application.

As requested by the Division and Office Directors, this communication is intended to emphasize the importance of the ADVANTAGE trial, study 102, in our review of the safety of Vioxx. The large size of the database at an approved chronic dose, without restrictions regarding aspirin, may address some of the issues raised earlier in the review. These concerns formed the basis for our initial request for the study report on November 27, 2000. The Advisory Committee concurred with the importance of such information at the February 8, 2001, meeting.

We consider review of the completed study report, with the appropriate safety analyses similar to those ultimately performed for the VIGOR database (e.g., including sub-analyses by low dose aspirin use and detailed analyses of cardiovascular and thrombotic events with case report forms), important for the current supplement.