Results for Study 096

Proportions of Patients Who Met ACR 70 Responder Index Criteria

During 12 Weeks of Study

(Modified Intention-to-Treat Approach)

ACR 70 Responder and Completers			
Treatment		Frequency † (%)	
Placebo		3/297 (1.01%)	
12.5 mg		5/146 (3.42%)	
25 mg		8/311 (2.57%)	
Naproxen		3/149 (2.01%)	
Between-Group Comparisons	Diff in Percent	(95% C.I.)	p-value §
25 mg vs. Placebo	1.56	(-0.53, 3.66)	0.156
12.5 mg vs. Placebo	2.41	(-0.75, 5.58)	0.092
Naproxen vs. Placebo	1.00	(-1.52, 3.53)	0.459
25 mg vs. 12.5 mg	-0.85	(-4.29, 2.58)	0.621
25 mg vs. Naproxen	0.56	(-2.30, 3.42)	0.698
12.5 mg vs. Naproxen	1.41	(-2.30, 5.12)	0.455
ACR 70 Responder: regardless of completion status			
Treatment		Frequency † (%)	
Placebo		5/297 (1.68%)	
12.5 mg		5/146 (3.42%)	
25 mg		9/311 (2.89%)	
Naproxen		3/149 (2.01%)	
Between-Group Comparisons	Diff in Percent	(95% C.I.)	p-value §
25 mg vs. Placebo	1.21	(-1.16, 3.58)	0.340
12.5 mg vs. Placebo	1.74	(-1.55, 5.03)	0.300
Naproxen vs. Placebo	0.33	(-2.36, 3.02)	0.912
25 mg vs. 12.5 mg	-0.53	(-4.02, 2.96)	0.776
25 mg vs. Naproxen	0.88	(-2.04, 3.81)	0.561
12.5 mg vs. Naproxen	1.41	(-2.30, 5.12)	0.455

† m/n where m=number of patients with response and n=total number of patients evaluated.

§ From Cochran-Mantel-Haenszel test with stratum (corticosteroid use) as a stratification factor.

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Results for Study 097

Proportions of Patients Who Met ACR 50 Responder Index Criteria

During 12 Weeks of Study

(Modified Intention-to-Treat Approach)

ACR 50 Responder and Completers

Treatment	Frequency [†] (%)
Placebo	30/295 (10.17%)
25 mg	52/315 (16.51%)
50 mg	51/295 (17.29%)
Naproxen	20/146 (13.70%)

Between-Group Comparisons	Diff in Percent	(95% C.I.)	p-value [§]
Rofecoxib[‡] vs. Placebo	6.72	(2.16, 11.27)	0.008
50 mg vs. Placebo	7.12	(1.59, 12.64)	0.012
25 mg vs. Placebo	6.34	(0.98, 11.70)	0.022
Naproxen vs. Placebo	3.53	(-3.03, 10.09)	0.264
50 mg vs. 25 mg	0.78	(-5.17, 6.73)	0.789
50 mg vs. Naproxen	3.59	(-3.46, 10.64)	0.331
25 mg vs. Naproxen	2.81	(-4.11, 9.73)	0.438

ACR 50 Responder: regardless of completion status

Treatment	Frequency [†] (%)
Placebo	30/295 (10.17%)
25 mg	53/315 (16.83%)
50 mg	54/295 (18.31%)
Naproxen	20/146 (13.70%)

Between-Group Comparisons	Diff in Percent	(95% C.I.)	p-value [§]
Rofecoxib[‡] vs. Placebo	7.37	(2.79, 11.95)	0.004
50 mg vs. Placebo	8.14	(2.53, 13.74)	0.005
25 mg vs. Placebo	6.66	(1.27, 12.04)	0.017
Naproxen vs. Placebo	3.53	(-3.03, 10.09)	0.264
50 mg vs. 25 mg	1.48	(-4.57, 7.52)	0.623
50 mg vs. Naproxen	4.61	(-2.51, 11.72)	0.221
25 mg vs. Naproxen	3.13	(-3.81, 10.07)	0.390

[†] m/n where m=number of patients with response and n=total number of patients evaluated.

[‡] Average 25 and 50 mg

[§] From Cochran-Mantel-Haenszel test with stratum (corticosteroid use) as a stratification factor.

Results for Study 097

Proportions of Patients Who Met ACR 70 Responder Index Criteria

During 12 Weeks of Study

(Modified Intention-to-Treat Approach)

ACR 70 Responder and Completers			
Treatment		Frequency † (%)	
Placebo		7/295 (2.37%)	
25 mg		7/315 (2.22%)	
50 mg		9/295 (3.05%)	
Naproxen		5/146 (3.42%)	
Between-Group Comparisons	Diff in Percent	(95% C.I.)	p-value §
Rofecoxib‡ vs. Placebo	0.25	(-1.90, 2.40)	0.826
50 mg vs. Placebo	0.68	(-1.94, 3.30)	0.623
25 mg vs. Placebo	-0.15	(-2.53, 2.23)	0.904
Naproxen vs. Placebo	1.05	(-2.37, 4.48)	0.511
50 mg vs. 25 mg	0.83	(-1.72, 3.38)	0.524
50 mg vs. Naproxen	-0.37	(-3.92, 3.17)	0.844
25 mg vs. Naproxen	-1.20	(-4.57, 2.17)	0.455
ACR 70 Responder: regardless of completion status			
Treatment		Frequency † (%)	
Placebo		7/295 (2.37%)	
25 mg		7/315 (2.22%)	
50 mg		9/295 (3.05%)	
Naproxen		5/146 (3.42%)	
Between-Group Comparisons	Diff in Percent	(95% C.I.)	p-value §
Rofecoxib‡ vs. Placebo	0.25	(-1.90, 2.40)	0.826
50 mg vs. Placebo	0.68	(-1.94, 3.30)	0.623
25 mg vs. Placebo	-0.15	(-2.53, 2.23)	0.904
Naproxen vs. Placebo	1.05	(-2.37, 4.48)	0.511
50 mg vs. 25 mg	0.83	(-1.72, 3.38)	0.524
50 mg vs. Naproxen	-0.37	(-3.92, 3.17)	0.844
25 mg vs. Naproxen	-1.20	(-4.57, 2.17)	0.455

† m/n where m=number of patients with response and n=total number of patients evaluated.

‡ Average 25 and 50 mg

§ From Cochran-Mantel-Haenszel test with stratum (corticosteroid use) as a stratification factor.

B. Labeling issues

The following addresses some of the labeling issues that are described in the sNDA review. Comments or changes appear for each section. Only sections for which changes from the presently approved label are included here.

Rheumatoid Arthritis (RA)

VIOXX has demonstrated significant reduction in joint tenderness/pain and joint swelling compared toplacebo. VIOXX was evaluated for the treatment of the signs and symptoms of RA in two 12-week placebo- and active-controlled clinical trials that enrolled a total of approximately 2,000 patients. VIOXX was shown to be superior to placebo on all primary endpoints (number of tender joints, number of swollen joints, patient and physician global assessments of disease activity). In addition, VIOXX was shown to be superior to placebo using the American College of Rheumatology 20% (ACR20) Responder Index, a composite of clinical, laboratory, and functional measures of RA. VIOXX 25 mg once daily and naproxen 500 mg twice daily showed generally similar effects in the treatment of RA. **A 50-mg dose once daily of VIOXX was also studied; however, no additional efficacy was seen compared to the 25-mg dose.**

Upper Endoscopy in Patients with Rheumatoid Arthritis

[ ]

Entry criteria for this study permitted enrollment of patients with active *Helicobacter pylori* infection, baseline gastroduodenal erosions, prior history of an upper gastrointestinal perforation, ulcer, or bleed (PUB), and/or age =65 years. However, patients receiving aspirin (including low-dose aspirin for cardiovascular prophylaxis) were not enrolled in this study.

[ ]

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Labeling

INDICATIONS AND USAGE
VIOXX is indicated:
For relief of the signs and symptoms of osteoarthritis.
For relief of the signs and symptoms of rheumatoid arthritis in adults.
For the management of acute pain in adults
For the treatment of primary dysmenorrhea.

PRECAUTIONS

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. **In post-marketing experience there have been reports of increases in plasma lithium levels.** Thus, when VIOXX and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Reviewers note: there are no additional changes in these sections.

ADVERSE REACTIONS
Gastrointestinal: cholecystitis, colitis, colonic malignant neoplasm, *duodenal perforation,* duodenal ulcer, *esophageal ulcer, gastric perforation, gastric ulcer,* gastrointestinal bleeding, *hepatitis,* intestinal obstruction, *jaundice,* pancreatitis.
Hemic and lymphatic: agranulocytosis, leukopenia, lymphoma, *thrombocytopenia.*
Immune System: anaphylactoid reaction, angioedema.
Nervous System: aseptic meningitis.
Psychiatric: confusion, hallucinations.
Skin and Skin Appendages: severe skin reactions, including Stevens-Johnson syndrome.
Urogenital System: acute renal failure, breast malignant neoplasm, *interstitial nephritis,* prostatic malignant neoplasm, urolithiasis, *worsening chronic renal failure.*
In 1-year controlled clinical trials and in extension studies for up to 86 weeks (approximately 800 patients treated with VIOXX for one year or longer), the adverse experience profile was qualitatively similar to that observed in studies of shorter duration.
Rheumatoid Arthritis

Approximately 1,100 patients were treated with VIOXX in the rheumatoid arthritis efficacy studies. The adverse experience profile was generally similar to that reported in the osteoarthritis studies.

Reviewers note: the adverse reaction section should include

DOSAGE AND ADMINISTRATION

VIOXX is administered orally. The lowest dose of VIOXX should be sought for each patient.

Osteoarthritis

The recommended starting dose of VIOXX is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

Rheumatoid arthritis

The recommended dose is 25 mg once daily. The maximum recommended daily dose is 25 mg.

Management of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended dose of VIOXX is 50 mg once daily. Use of VIOXX for more than 5 days in management of pain has not been studied (see

VIOXX tablets may be taken with or without food.

Reveiwers note: the dosage section should include the following under RA:

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

/s/

Joel Schiffenbauer
12/20/01 02:07:21 PM
MEDICAL OFFICER

Maria Villalba
12/20/01 04:48:35 PM
MEDICAL OFFICER

Lawrence Goldkind
12/21/01 03:42:47 PM
MEDICAL OFFICER

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XII. Appendix II

VIOXX SAFETY IN RA EFFICACY STUDIES

I. Integrated Review of Safety

A. Brief Statement of Conclusions

1. Overall safety in the RA application database

There were a total of eight deaths: five on rofecoxib, two on naproxen and one on placebo. There were two, one and one cardiovascular deaths in the rofecoxib 50 mg, rofecoxib 25 mg and naproxen groups, respectively. The pattern of adverse events, discontinuations due to adverse events, laboratory AE's and vital signs was consistent with data submitted in the original NDA submission. .

2. Cardiovascular safety in the RA application database.

There were 6 MI 's (one fatal) in the rofecoxib 25 mg group, 5 MI's (one fatal) and 1 sudden death in the rofecoxib 50 mg group and one fatal MI in the naproxen group. Although the number of events is small, the higher incidence of MI's on rofecoxib as compared to naproxen is consistent with findings in VIGOR and ADVANTAGE. Consistent with VIGOR but different from ADVANTAGE, there was no excess of strokes in the naproxen group in the RA database.

Hypertension related events were observed two to three times more often in each of the rofecoxib arms, as compared to the naproxen arm or placebo. A higher percentage of patients presented important increase of blood pressure and required concomitant antihypertensive medication and/or discontinued from each of the rofecoxib arms compared to the naproxen arm. The numbers of patients with edema-related events were higher in the rofecoxib 25 and 50 mg groups as compared to naproxen. These findings were consistent in the placebo-controlled treatment phase and in the long-term exposure databases.

Three CHF related events occurred during one year studies - all in the rofecoxib 50 mg group -. Two additional cases occurred in the extension period, one in rofecoxib 25 mg and one in rofecoxib 50 mg. The number of CHF events is small to draw definitive conclusions but is consistent with VIGOR in which rofecoxib 50 mg was associated with higher risk of developing CHF related events than naproxen.

3. Signal of increased risk of fractures with rofecoxib as compared to naproxen.

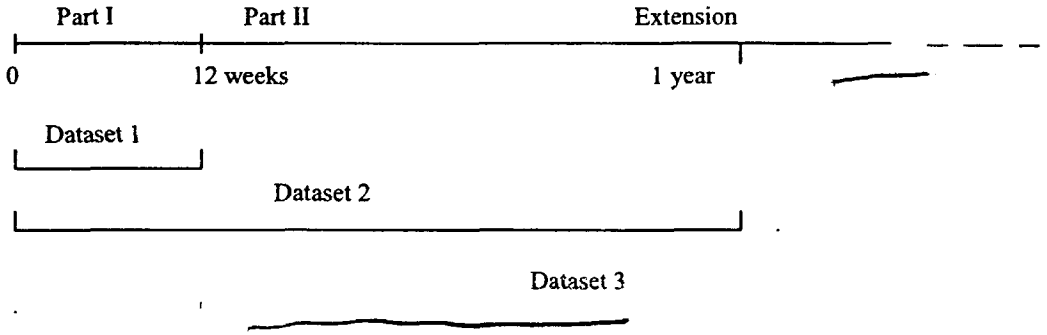
More fractures occurred in the rofecoxib arms (9 and 3 for rofecoxib 50mg and 25 mg respectively) as compared to the naproxen arm (no fractures). This trend was consistent with the VIGOR study. However, in a larger safety database of approximately 3000 patients exposed to either rofecoxib 25 mg or placebo for one year there was no differences in the numbers of fractures.

B. Description of Patient Exposure

Studies reviewed as part of this application include 068, 096, 097 and 98/103. Some of these protocols had a somewhat complicated study design, with some patients switching treatments between parts. A patient may have been counted in different treatment groups for different parts of a study.

The RA safety database contains approximately 2000 patients exposed to rofecoxib (12.5, 25 and 50 mg); 550 patients exposed to naproxen and 1000 patients exposed to placebo. The bulk of the exposure was to 3 and 6 months of treatment. Approximately 1500 patients were exposed to rofecoxib 25 mg (n= 797) and 50 mg (n= 677) in 3-month placebo controlled studies. Approximately 180, 140 and 80 patients were exposed to rofecoxib 25mg, rofecoxib 50mg and naproxen 1000 mg respectively, for one year

The RA safety database was presented by the sponsor divided into three datasets:



- Dataset 1: placebo controlled phase: Part I of studies 068 (8 weeks) and 096 and 097 (12 weeks) plus entire protocol 098.103 (12-weeks);
- Dataset 2: long-term continuous therapy period including the initial 12 weeks (analyzed under Dataset 1) plus Part II of studies 096 and 097, of which some patients received treatment for up to one year

[ ]

A patient who received more than one dose would be reported under each applicable dosage row for the duration that the given dose was taken. Therefore, the same patient may appear in the three different datasets.

Reviewer's comment:

The most relevant of the three datasets appears to be the one-year comparative data to naproxen, although this dataset includes studies of 8 to 12 weeks duration. Placebo-controlled data are important but limited to 12 weeks.

Most of the tables presented by the sponsor and tables in this review are based on crude rates using the number of randomized patients as the denominator (crude rate). However,

since not all randomized patients actually completed the studies, for events of particular interest, it is more adequate to compare event rates based on true exposure.

Patient years of exposure for each treatment group, as calculated by the sponsor by adding the days on which patients are recorded in the data base as having taken study medication and dividing by 365 days/year, are presented in Table 1. Of note, because of the complexity of patient accounting in study 068, at the reviewer's request the sponsor provided a separate listing of patient/years of exposure for study 068.

Protocol 068, Part I (derived from CSR Table 36):
- **Rofecoxib — ng – 22.5 patient years**
- **Rofecoxib 25 mg – 24.3 patient years**
- **Rofecoxib 50 mg – 22. 5 patient years**
- **Placebo - 22.8 patient years**

Protocol 068, Part II (derived from CSR Table 14):
- **Rofecoxib 25 mg 161.7 patient years**
- **Rofecoxib 50 mg – 144.6 patient years**
- **Naproxen 1000 mg – 59.2 patient years**

Protocol 068, Extension 10 and 20 (derived from CSR Table 6):
- **Rofecoxib 25 mg – 115.9 patient years**
- **Rofecoxib 50 mg – 100.1 patient years**
- **Naproxen 1000 mg – 37.8 patient years**

Table 1. Patient years of exposure RA database.

Assigned therapy	Patient years of exposure in studies 096, 097 and 098/103[1]	Patient years of exposure in study 068[2]	Patient years of exposure in the complete database
Placebo	160	22.5	183
Rofecoxib 12.5	29	-	29
Rofecoxib 25	501	301.9	802
Rofecoxib 50	430	267.2	697
Naproxen	406	97	503

[1,2] Provided by sponsor, submitted 8/13/01 ([1]) and 9/20/01 ([2]).

Reviewer's comment: While adequate for common events such as edema, less common but severe events can not be well assessed in databases of this size.

C. Methods and specific Findings of Safety Review

The safety review was conducted by corroboration of listings of deaths, serious adverse events (AE's), discontinuations due to AE's, most common AE's, laboratory AE's and vital signs in summary tables against individual study reports. In view of the cardiovascular signal observed in prior rofecoxib databases (VIGOR and ADVANTAGE) particular interest was placed in the review of events related to the cardiovascular system.

D. Safety results

Demographic characteristics of the population.

No significant between-group differences were observed in baseline demographics between treatment groups in three different datasets. Approximately eighty percent of patients were women; 70 to 80% were Caucasian; mean patient age was 54 years (ranging from 20 to 87 years).

Of note, more patients had a prior history of gastric ulcer in the naproxen group (8.5%) as compared to the rofecoxib 25 mg (6.8%) and the rofecoxib 50 mg group (6.2%) as well of history of gastritis (5.4%, 3.3% and 4.3% in the naproxen, rofecoxib 25 and rofecoxib 50 mg, respectively). More patients had a history of lower extremity edema in the rofecoxib 25 mg group (5.1%) as compared to the rofecoxib 50 mg (1.8%) and naproxen group (2.5%). More patients had a prior history of hypertension in the rofecoxib 25 mg group (24.5%) as compared to the rofecoxib 50mg group (23.3%) and naproxen group (21.5%).

More patients had used systemic corticosteroids within 30 days prior to enrollment in the naproxen group (56.8%) as compared to the rofecoxib 25 mg (42.9%) and rofecoxib 50 mg group (53.6%).

Of note, patients with recent history of myocardial infarction or stroke and those deemed by the investigator to require low dose aspirin for cardiovascular prophylaxis were excluded during the enrollment period of all studies, except Protocol 096. Protocol 097 and the extension to Protocol 068 were subsequently amended to allow concomitant low-dose aspirin, as medically indicated, for cardioprophylaxis.

1. Deaths

There were a total of eight deaths: five on rofecoxib, two on naproxen and one on placebo. None of the deaths were considered by the investigator to be treatment related. There were two cardiovascular deaths in the rofecoxib 50 mg group, one in the rofecoxib 25 mg group and one on naproxen.

Table 2. NDA 21-042/s012. Deaths

AN	Age/sex	Cause of death	Relative Day #	Treatment
096 3669 068 2285	75F 72M	Lung carcinoma, Jakob-Creuzfeldt	56 344	Rofecoxib 25 mg
0963185*		Cardiac Arrest. MI		
096 2190 068 2568	69F 67F	Pneumonitis Lung carcinoma	17 331	Rofecoxib 50 mg
097 6354*		Fatal MI		
0975609*		Sudden death		
103 15128	46M	Liver failure	46	Naproxen 1000 mg
0975194*		Fatal MI		
097 5093	68F	Sepsis	88	Placebo

Source Table B-31, ISS; narratives and CRFs. * Identified by sponsor in 8/13/01 submission; CRF's for these cases are not available.

2. Serious adverse events (AE's)

2.1 Serious AE's in Placebo controlled phase (Dataset 1). (Table 3)

The number of patients with one or more SAE's in the 12-week placebo-controlled phase (dataset 1) were small and similar in all treatment groups (2.4% for rofecoxib 25 and 50 and placebo; 4.1% for naproxen). SAE's with incidence of 1% or more were in the urogenital system for naproxen (1%) and the musculoskeletal system for rofecoxib 50 mg (1.2 %). There were no differences in SAE's related to the digestive or the cardiovascular system between treatment groups.

2.2 Serious AE's in Dataset 2 (Table 4)

The number of patients with one or more SAE's in the one-year dataset was 5.9%, 9.4% and 9.5% for rofecoxib 25mg, rofecoxib 50 mg and naproxen. Most frequent serious events (2% or more in at least one treatment group) by body systems were in the cardiovascular, digestive and musculoskeletal systems.

2.3 Serious AE's in Dataset 3 (Table 5).

The number of patients with one or more SAE's in the Part II and extension studies dataset was 8.5%, 10.3% and 8.6%. The most frequent SAE's in this dataset were in the cardiovascular and musculoskeletal systems.

Table 3. Serious AE's and discontinuations by body system in RA studies of up to 12-week duration, Dataset 1. (Source: sponsor's table 17 and 19, RA SUR).

	Placebo (N=989)		Rofecoxib 25 (N=797)		Rofecoxib 50 (N=677)		Naproxen 1000 (N=516)	
	SAE n (%)	Discont n (%)	SAE n (%)	Discont n (%)	SAE n (%)	Discont n (%)	SAE n (%)	Discont n (%)
Patients with one or more event	24 (2.4)	40 (4.0)	18 (2.3)	38 (4.8)	16 (2.4)	47 (6.9)	21 (4.1)	40 (7.8)
Body as a whole	3	9	2	6	1	12 (1.8)	1	8 (1.6)
Cardiovascular	2	4	6	8 (1.0)	2	3	3	1
Digestive	2	10 (1.0)	2	10 (1.3)	3	17 (2.5)	3	24 (4.7)
Ear nose and throat	-	2	-	2	1	1	1	-
Hepatobiliary	3	-	-	-	-	-	1	-
Musculoskeletal	3	3	3	3	8	4	3	2
Nervous	2	2	-	4	-	3	1	-
Psychiatric		-		2		3		-
Respiratory	3	-	1	-	2	-	2	-
Skin And Skin Append	1	4	2	-	1	4	1	2
Urogenital System	7	4	3	2	1	-	5 (1)	1

SAE: serious adverse events. Disc: discontinuations. N= patients randomized. n= events. Percentages appear only for those events with at least 1% incidence.

Table 4. Serious AE's and discontinuations by body system in RA studies of 8-week to 1 year duration (Dataset 2). (Source: sponsor's table 26 and 28 RA SUR)

	Rofecoxib 25 (N=491)		Rofecoxib 50 (N=458)		Naproxen 1000 (N=296)	
	SAE n (%)	Discont n (%)	SAE n (%)	Discont n (%)	SAE n (%)	Discont n (%)
Patients with one or more event	29 (5.9)	46 (9.4)	43 (9.4)	62 (13.5)	28 (9.5)	37 (12.5)
Body as a whole	1	9 (1.8)	4	12 (2.6)	2	8 (2.7)
Cardiovascular	5 (1.0)	11 (2.2)	8 (1.7)	7 (1.5)	6 (2.0)	2
Digestive	3	11 (2.2)	5 (1.1)	23 (5.0)	7 (2.4)	19 (6.4)
Ear nose and throat	-	1	-	1	1	-
Hematologic & lymphatic	-	-	1	-	-	2
Musculoskeletal	9 (1.8)	3	19 (1.8)	4	5 (1.7)	3 (1.0)
Nervous	2	5 (1.0)	2	4	3	-
Psychiatric	1	1	-	4	-	-
Respiratory	3	2	6	3	2	-
Skin And Skin Append	3	-	3	6 (1.3)	3 (1.0)	1
Urogenital System	3	3	5 (1.1)	1	2	2

SAE: serious adverse events. Disc: discontinuations. N= patients randomized. n= events. Percentages appear only for those events with at least 1% incidence.

Table 5. Serious AE's and discontinuations due to AE's by body system in RA extension studies. Dataset 3. (Source: sponsor's table 35 and 37 RA SUR)

	Rofecoxib 25 (N=823)		Rofecoxib 50 (N=729)		Naproxen 1000 (N=557)	
	SAE n (%)	Discont n (%)	SAE n (%)	Discont n (%)	SAE n (%)	Discont n (%)
Patients with one or more event	72 (8.7)	62 (7.5)	77 (10.6)	68 (9.3)	48 (8.6)	53 (9.5)
Body as a whole	5	7	10 (1.4)	7 (1.0)	2	6 (1.1)
Cardiovascular	14 (1.7)	15 (1.8)	17 (2.3)	16 (2.2)	13 (2.3)	7 (1.3)
Digestive	5	14 (1.7)	9 (1.2)	24 (3.3)	10 (1.8)	25 (4.5)
Ear nose and throat	2	2	1	2	2	1
Hematologic & lymphatic	3	2	2	1	2	5
Musculoskeletal	23 (2.8)	3	20 (2.7)	1	11 (2.0)	4
Nervous	5	5	5	3	4	1
Psychiatric	1	-	2	3	-	-
Respiratory	5	2	6	3	1	-
Skin And Skin Append	9	5	6 (1.1)	7 (1.0)	3	2
Urogenital System	10(1.2)	6	12 (1.6)	3	2	2

SAE: serious adverse events. Disc: discontinuations. N= patients randomized. n= events. Percentages appear only for those events with at least 1% incidence.

3. Discontinuations due to AE's

3.1 Discontinuations due to AE's in the placebo-controlled phase (Table 3)

The number of patients who discontinued due to one or more AE's was a little higher for rofecoxib 50 mg and naproxen groups (9 % and 8 %, respectively), compared to the placebo and rofecoxib 25 mg groups (4 % and 5 %, respectively). Of note, the body system with most discontinuations was the digestive, for all treatment groups, including placebo. The vast majority of the events leading to discontinuation were not considered serious by the investigator.

3.2 Discontinuations due to Adverse Events in Dataset 2 (Table 4)

In studies of up to one year duration, the number of patients discontinued due to AE's was 13.5%, 9.4% and 12.5% in the rofecoxib 50 mg, rofecoxib 25 mg and naproxen, respectively. The most frequent events were in the body as a whole, cardiovascular and digestive systems.

3.3 Discontinuations due to AE's in Part II and extension studies (Dataset 3) (Table 5)

In the extension studies dataset, the number of patients who discontinued due to AE's was 9.4%, 13.5 and 12.5% in the rofecoxib 25 mg group, rofecoxib 50 and narproxen groups respectively. The most frequent events leading to discontinuation were in the cardiovascular and digestive systems.

4. Most common AE's

4.1 Most common clinical AE's

In the placebo controlled phase of the RA studies, 60 to 66% of patients had at least one adverse experience. In the one-year dataset, 81 to 85% of patients had at least one AE. In the extension studies, approximately 76 % of patients had at least one AE. The most frequent events were in the body as a whole system (22-26% of patients in the placebo controlled phase; 42-44% in the one year database and 31 to 37% in the extension studies) and in the digestive system (20.8%, 23.3 %, 30.6% and 39.5% in the placebo, rofecoxib 25 mg, rofecoxib 50 mg and naproxen groups, respectively in the placebo-controlled phase; 36% to 48 % in the one-year dataset and 24% to 30 % in the extension studies).

Reviewer's comment: In summary, there were no substantial differences in the total number of serious adverse events, discontinuations due to adverse events and common adverse events between treatment groups in each of the three datasets, particularly the long term datasets.

5. Laboratory Adverse events

Table 6. Laboratory adverse experiences in the RA database (source: sponsor's tables)

	Placebo n/N	%	Rofe 25 n/N	%	Rofe 50 n/N	%	Naproxen n/N	%
Placebo controlled phase (up to12 weeks)								
Any lab AE	92/989	**9.4**	85/797	**10.7**	90/677	**13.3**	76/516	**14.8**
Discont due to lab AE	-		2	**0.3**	3	**0.4**	2	**0.4**
Long-term continuous (up to one-year)								
Any lab AE			94/491	**19.2**	105/458	**23.0**	60/296	**20.3**
Discontinuations due to lab AE			4	**0.8**	7	**1.5**	3	**1.0**
Continuation and extension periods (—— ——								
Any lab AE			135/823	**16.4**	149/729	**20.5**	97/557	**17.4**
Discontinuations due to lab AE			9	**1.1**	9	**1.1**	3	**0.5**

There were no serious laboratory adverse events. Very few patients discontinued due to laboratory adverse events. Alanine amino transferase and/or Aspartate amino transferase increase were the most common laboratory abnormalities (in approximately 2% of patients in the placebo-controlled phase and 3 to 8% in the one-year and extension datasets). Increased creatinine was presented by 0.1%, 0.6%, 0.6% and 0.2% of patients in the placebo, rofecoxib 25, rofecoxib 50 and naproxen groups, respectively in the placebo-controlled phase and in 0.6, 2.2% and 0% of patients in the rofecoxib 25, 50 and naproxen groups respectively, in the one-year dataset. Decreased hematocrit was presented by 1.1%, 2.6%, 5% and 6.2% of patients in the placebo, rofecoxib 25, rofecoxib 50 and naproxen groups, respectively in the placebo-controlled phase and in 4.3, 9% and 7.5% of patients in the one-year dataset.

Reviewer's comment: There were no new safety signals related to laboratory AE's in this database.

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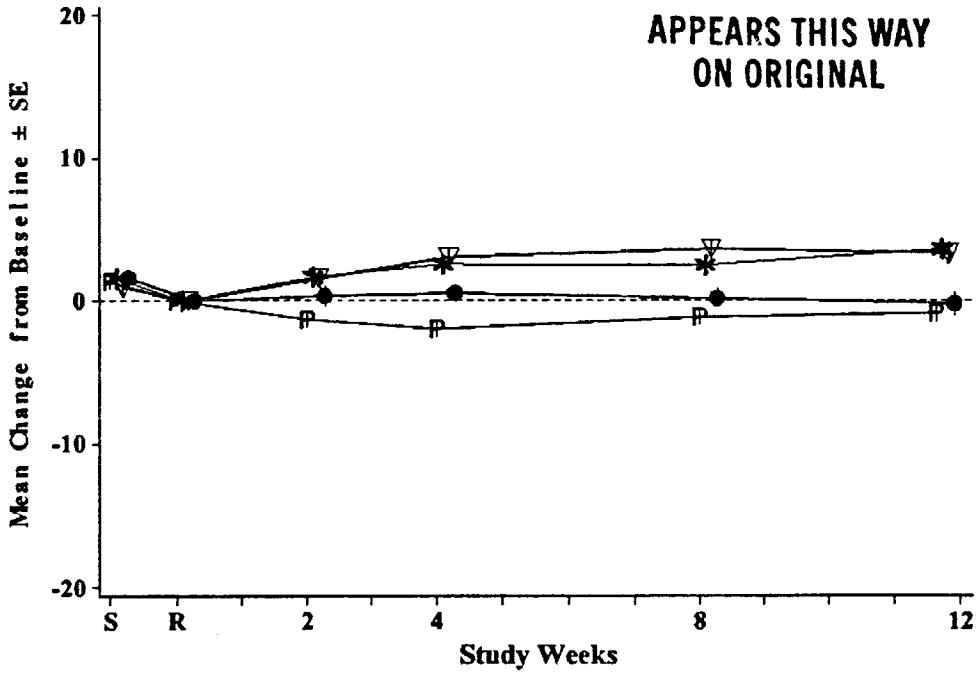
6. Vital signs

Reviewer's comment: The sponsor has provided summary reports and mean changes from baseline for systolic and diastolic blood pressure plotted over time. Listing of actual values and statistical analyses of differences between different treatments have been requested.

6.1 Blood pressure changes in 12-week placebo-controlled studies.

Figure 1. Mean change in systolic blood pressure (SBP) in 12-week dataset.

Rheumatoid Arthritis (Protocols 068, 096, 097, 098 and 103)
(All Patients)
(Placebo Controlled Period)



P=placebo ✱=Rofecoxib 25mg ▽=Rofecoxib 50mg ●=Naproxen 1000mg
S:Screening, R:Randomization
all patients: Systolic Blood Pressure (mm Hg)

In the 12-week dataset, mean change from baseline in SBP was **3.6 mmHg** in the rofecoxib 50 and 25 mg groups at 12 weeks compared to no change in the naproxen and placebo groups.

As per time-plot provided by the sponsor, mean change from baseline in DBP appears to be approximately **2.5 mmHg** in the rofecoxib 50 group. Changes are less obvious for the 25 mg group. There were no changes in the placebo and naproxen groups.

6.2 Blood pressure changes in studies of up to one year (Dataset 2)

The sponsor states that overall effects with rofecoxib in mean SBP over time were generally an increase of **4- to 6-mmHg**. As per the figure presented by the sponsor, the change from baseline for naproxen did not exceed 1 mmHg, however the 95% CI are wide and seem to overlap at several time points with rofecoxib 25 and 50 mg. For mean DBP, the 50-mg treatment group showed changes from baseline up to **2.2 mm Hg**. The 25-mg rofecoxib and naproxen groups showed no clear trend for change. Because of decreasing patient numbers, interpretation of later time points must be made with caution: at 52 weeks, data were available for 123, 88, and 27 patients in the 25-mg and 50-mg rofecoxib and naproxen treatment groups, respectively.

> *Reviewer's comment: It appears that rofecoxib at both 25 and 50 mg are associated with larger change in BP, particularly systolic BP than naproxen and placebo. Statistical analyses have been requested.*

6.3 ECG

Formal analysis of ECG data were not conducted. AE based on abnormal ECG findings were captured in the database and register on clinical AE count tables.

7. Cardiovascular safety in the current submission

> *Reviewer's comment: Renal/vascular side effects of NSAIDs related to fluid retention and elevations in blood pressure were some of the pre-specified safety analyses in this application. Serious cardiovascular thrombotic events were not pre-specified in the original protocols but were conducted by the sponsor at the Agency's request.*

7.1 Serious cardiovascular thrombotic events

Investigator reported potentially serious cardiovascular thrombotic (SCV/T) events as submitted in the SUR for this application are presented in Table 7.

> *Reviewer's comment: The procedure for evaluation of SCV/T events was the same as the followed in VIGOR and ADVANTAGE. The list of "investigator reported serious cardiovascular thrombotic AE's" includes terms that may actually be non-thrombotic (for complete list, the reader is referred to this medical officer's review of the Complete Response to Approvable letter for NDAs 21-042/007). Similar to what was done in VIGOR and ADVANTAGE, a Merck's representative reviewed the list of investigator reported events and referred the potential cases to a cardiovascular adjudication committee.*
>
> *Of note, SCV/T events were referred to the CV adjudication committee from all but study 068. Only deaths were referred for adjudication from study 068.*

Review of SCV/T by this medical officer found that the sponsor's summary tables for the initial submission (2/28/01) and the safety update report (6/22/01) (Table 7) did not include all events listed in individual studies. At the Agency's request the sponsor provided a final updated listing of these events (8/13/01). Table 8 lists SCV/T events missing from the 2/28 and 6/22/01 submissions.

Table 7. Listing of Investigator Reported Serious Cardiovascular thrombotic adverse experiences (tableB76 orig. submission and T64 SUR)

AN	Age/sex	Assigned therapy (mg/day)	Diagnosis (rel day onset)	Adjudication by CV committee	APTC event
Patients identified in initial submission					
068 2368	82 M	Rofecoxib 25	unstable angina	Not referred for adjudication	
2683	61 F	Rofecoxib 50	CVA		
2839	M	Rofecoxib 50	CVA		
2267	73 F	Rofecoxib 50	acute MI		
2346	M	Rofecoxib 50	MI and CVA		
2369	77 F	Naproxen 1000	MI		
2477	75 M	Naproxen 1000	angina pectoris		
2552	56 M	Naproxen 1000	unstable angina		
2627	65 F	Naproxen 1000	unstable angina		
0963407	57 F	Rofecoxib 12. 5	acute MI	Yes	Yes
3545	61 F	Rofecoxib 12. 5	TIA	Yes	No
4105	68 M	Rofeocixb 12. 5	MI	Yes	Yes
4043	70 F	Rofecoxib 25	acute MI	Yes	Yes
3151	F	Rofecoxib 25	Unstable angina	Yes	No
3397	F	Rofecoxib 25	lacunar infarction, TIA	Yes	No
4266	M	Rofecoxib 50	MI	Yes	Yes
97 6262	F	Naproxen	unstable angina	No	No
98 14062	75 F	Placebo	CVA	yes	yes
Patients identified in SUR					
0963122	F	Rofecoxib 25	MI	Yes	Yes
3457	F	Rofecoxib 25	TIA	Yes	No
0975057	F	Rofecoxib 50	CVA	Yes	Yes
5425	M	Rofecoxib 50	Unstable angina	No	No
6188	M	Rofecoxib 50	MI	Yes	Yes
6354	M	Rofecoxib 50	Fatal MI	Yes	Yes
5609		Rofecoxib 50	Sudden death	Yes	Yes
6354		Rofecoxib 50	Fatal MI	Yes	Yes
5624		Rofecoxib 50	Ischemic heart dz	No	No
5627		Rofecoxib 50	CHF	Yes	Yes
6267		Naproxen	Lower extr isch	No	No
5157	M	Naproxen	Angina pectoris	No	No
5194	F	Naproxen	Fatal MI	Yes	Yes
103 15126	38 F	Placebo	Venous occlusion	No	no

Table 8. Additional Investigator Reported Serious Cardiovascular Thrombotic events (submitted 8/13/01), missing from previous submissions.

AN	Age/sex	Assigned therapy	Diagnosis (rel day onset)	Adjudicated by CV committee	APTC event
068 2735	68 F	Rofecoxib 50	CVA	Not referred for adjudication	
2034	58 M	Rofecoxib 25	Arterial occlusion		
2368		Rofecoxib 25	Angina pectoris		
2611		Rofecoxib 25	Arterial thrombosis		
2662	75 F	Rofecoxib 50	Carotid art obstr		
2885	58 F	Rofecoxib 50	Carotid art obstr		
0963185	61 M	Rofecoxib 25	Cardiac arrest. MI	Yes	Yes
3618	63 F	Rofecoxib 25	MI	No	Yes
4271	65 F	Rofecoxib 25	MI	No	Yes
4653	70 F	Rofecoxib 25	Pulm. embolism	No	No
3497		Naproxen	Coronary art dz	No	No
4460		Rofecoxib 25	Ventricular arrhythmia	No	No
0975084	67 F	Rofecoxib 50	TIA		
5934	63 F	Rofecoxib 25	Non Q wave MI	Pending	Yes
5918		Rofecoxib 50	DVT	Yes	No
6147		Naproxen	Peripheral vasc dis	No	No

Of note, all but two SCV/T events missing from prior submissions were on the rofecoxib 25 or 50 mg groups. Most of these events occurred after 1 or ~ years of ongoing therapy.

It is unclear why two MI's that were not adjudicated (on rofecoxib 25 mg) were considered APTC events. Also, a non Q wave MI which adjudication was pending (0975084) was considered an APTC event.

7.1.1 Sponsor's analyses of Serious CV/Thrombotic events

Table 9. Sponsor's analysis of investigator SCV/T and APTC events in RA studies (8/13/01).

Rates of Investigator-Reported Thromboembolic and APTC Events (by Assigned Treatment) (Protocols 068, 096, 097, and 098/103)

Assigned Therapy	Patient-Years at Risk	Number of Investigator-Reported Events†	Rate of Investigator-Reported Adverse Experiences† (per 100 Patient-Years at Risk)	APTC Events‡	Rate of APTC Events (per 100 Patient-Years at Risk)
Placebo	183	2	1.1	1	0.5
Rofecoxib 12.5 mg	29	3	10.3	2	6.9
Rofecoxib 25 mg	861	13	1.5	4	0.5
Rofecoxib 50 mg	753	17	2.3	11	1.5
Rofecoxib treatment groups combined	1643	33	2.0	17	1.0
Naproxen 1000 mg	522	11	2.1	3	0.6

† Includes events reported by investigators under terms prespecified as potentially thromboembolic.
‡ Ascertainment of Anti-Platelet Trialists Collaboration (APTC) events based on investigator-reported term(s) where adjudication was not performed (Protocol 068) or is pending. Otherwise APTC events were based on the adjudicated diagnosis.
Note: Protocol 068 was initiated prior to the program-wide cardiovascular-event monitoring.

Cumulative Data Source: [48; 23; 27; 35; 41; 461

Reviewer's comment: The sponsor's analysis indicates a higher risk of developing APTC events for rofecoxib 50 mg as compared to naproxen or placebo. The risk does not appear higher in the rofecoxib 25 mg group and the event rate for the rofecoxib 12.5 mg group appears to be excessively high. The size of this database does not allow adequate assessment of CV safety.

Of note, the patient years at risk in this table do not match the sum of patient-years at risk as presented in Table 1 of this review. Additionally, some of the APTC events have not been confirmed (only deaths from 068 were referred for adjudication; two MI in the rofecoxib 25 mg group were not confirmed and one was pending).

7.1.2 FDA re-analysis of Serious CV/Thrombotic events

A re-analysis of SCV/T events by FDA using updated data as per the 8/13/01 submission and exposure data presented in Table 1 of this review was consistent with the sponsor's analyses. CRF' from additional cases submitted on 8/31/01 were not available for review.

Table 10. Summary of Serious CV/Thrombotic investigator reported events in RA database (FDA analysis as per 8/31/01 submission and Table 1 of this review).

Events	Placebo	12.5	25	50	Naproxen
	Patient/years at risk[1]				
	183	29	802	697	503
Cardiac	-	2	12	9	8
Sudden death	-	-	-	1	1
MI fatal/nonfatal	-	2	6	5	1
Unstable angina	-	-	3	2	5
Other[2]	-	-	3	1	1
Cerebrovascular	1	1	2	7	-
CVAccident	1	1	2	4	-
TIA	-	-	-	1	-
Other[3]	-	-	-	2	-
Peripheral	1	-	1	1	2
Venous occlusion	-	-	-	1	-
Pulmonary embolism	-	-	1	-	-
Arterial ischemia	-	-	-	-	-
Total number of patients with events	2	3	15	17	10
Risk per 100 pt. years	**0.5**	**6.9**	**1.9**	**2.4**	**2.0**

Includes studies 068, 096, 097, 098 and 103. Source, Tables 1, 7 and 8 of this review. [1] Patient years at risk calculated per Table 1. [2] Other cardiac: arterial occlusion, arterial thrombosis, ventricular arrhythmia, ischemic heart disease. [3] Other cerebrovascular: carotid obstruction, carotid artery disease.

Reviewer's comment:

Consistent with VIGOR and ADVANTAGE, there were more MI on rofecoxib 50 mg (n=5) and 25 mg (n= 6) than on naproxen (n= 1). Consistent with VIGOR but different from ADVANTAGE, there was no excess of strokes in the naproxen group.
Of note, patients with a recent history of MI or stroke and patients deemed by the investigator to require low dose ASA for cardiovascular prophylaxis have not been allowed in most of the studies. Although the number of events is small, the consistency of the trend in different studies is of concern.

The number of adjudicated CV/T events and APTC events in this database is too small to adequately assess cardiovascular safety.

7.2 Edema related events.

In all three datasets (placebo controlled phase, long-term continuous and continuation and extension phase) the number of patients with edema related events was higher in the rofecoxib 25 and 50 mg treatment groups, compared to naproxen.

Table 11. Edema-related AE's, 12-week Placebo Controlled periods (Source Table 20 SUR)

	Cumulative Data							
			Rofecoxib					
	Placebo (N=989)		25 mg (N=797)		50 mg (N=677)		Naproxen (N=516)	
	n	(%)	n	(%)	n	(%)	n	(%)
Edema And Related Terms	**15**	**(1.5)**	**39**	**(4.9)**	**23**	**(3.4)**	**9**	**(1.7)**
Edema	2	(0.2)	5	(0.6)	7	(1.0)	3	(0.6)
Fluid Retention	2	(0.2)	4	(0.5)	2	(0.3)	0	(0.0)
Lower Extremity Edema	8	(0.8)	23	(2.9)	11	(1.6)	5	(1.0)
Peripheral Edema	3	(0.3)	8	(1.0)	3	(0.4)	1	(0.2)
Discontinued Due To Edema And Related Terms	**2**	**(0.2)**	**1**	**(0.1)**	**3**	**(0.4)**	**0**	**(0.0)**

Table 12. Edema related AE's in one year database (Table 29 SUR)

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	Cumulative Data					
	Rofecoxib					
	25 mg (N=491)		50 mg (N=458)		Naproxen (N=296)	
	n	(%)	n	(%)	n	(%)
Edema And Related Terms	**36**	**(7.3)**	**30**	**(6.6)**	**15**	**(5.1)**
Edema	4	(0.8)	10	(2.2)	2	(0.7)
Fluid Retention	2	(0.4)	4	(0.9)	1	(0.3)
Lower Extremity Edema	22	(4.5)	13	(2.8)	13	(4.4)
Peripheral Edema	9	(1.8)	4	(0.9)	0	(0.0)
Discontinued Due To Edema And Related Terms	**1**	**(0.2)**	**4**	**(0.9)**	**1**	**(0.3)**

Table 13. Edema- related events. Continuation and extension periods (Dataset 3) (Table 38 SUR)

	Cumulative Data					
	Rofecoxib					
	25 mg (N=823)		50 mg (N=729)		Naproxen (N=557)	
	n	(%)	n	(%)	n	(%)
Edema And Related Terms	**49**	**(6.0)**	**32**	**(4.4)**	**20**	**(3.6)**
Edema	5	(0.6)	11	(1.5)	4	(0.7)
Fluid Retention	4	(0.5)	5	(0.7)	1	(0.2)
Lower Extremity Edema	33	(4.0)	15	(2.1)	14	(2.5)
Peripheral Edema	9	(1.1)	2	(0.3)	1	(0.2)
Discontinued Due To Edema And Related Terms	**1**	**(0.1)**	**3**	**(0.4)**	**2**	**(0.4)**

Table 14. Summary of Edema related events in RA application (includes terms such as edema, fluid retention, lower extremity edema, peripheral edema)

	Placebo n/N	%	Rofe 25 n/N	%	Rofe 50 n/N	%	Naproxen n/N	%
Placebo controlled phase (12 weeks)	15/989	**1.5**	39/797	**4.9**	23/677	**3.4**	9/516	**1.7**
Long-term continuous (13 weeks to one-year)	-		36/491	**7.3**	30/458	**6.6**	15/296	**5.1**
Continuation and extension periods	-		49/823	**6.0**	32/729	**4.4**	20/557	**3.6**

Reviewer's comment: In all three datasets the incidence of edema-related events was consistently higher although not statistically significantly different in the rofecoxib 25 and 50 mg groups as compared to naproxen. The difference was more marked in the 12-week placebo controlled phase. Review of the baseline demographics indicates that more patients in the rofecoxib 25 mg group (5.1 %) had a prior history of edema compared to the rofecoxib 50 mg (1.8%) and naproxen groups (2.5%), which may explain in part why more patients in the rofecoxib 25mg group had more edema-related events than the 50 mg group.

7.3 Hypertension-related events

Hypertension related events were observed two to three times more often in each of the rofecoxib arms, as compared to the naproxen arm or placebo. A higher percentage of patients presented important increase of blood pressure and required concomitant medication in the rofecoxib treatment groups compared to the naproxen group. More patients discontinued due to HTN related events from each of the rofecoxib groups as compared to the naproxen group.

Table 15. Hypertension related events in 12-week placebo controlled period(Source Table 21 SUR)

	Cumulative Data							
			Rofecoxib					
	Placebo (N=989)		25 mg (N=797)		50 mg (N=677)		Naproxen (N=516)	
	n	(%)	n	(%)	n	(%)	n	(%)
Hypertension And Related Terms	**22**	**(2.2)**	**49**	**(6.1)**	**43**	**(6.4)**	**10**	**(1.9)**
Blood Pressure Increased	3	(0.3)	9	(1.1)	3	(0.4)	0	(0.0)
Diastolic Hypertension	2	(0.2)	0	(0.0)	1	(0.1)	0	(0.0)
Hypertension	16	(1.6)	37	(4.6)	39	(5.8)	10	(1.9)
Uncontrolled Hypertension	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Discontinued Due To Hypertension And Related Terms	**1**	**(0.1)**	**2**	**(0.3)**	**2**	**(0.3)**	**1**	**(0.2)**

Table 16. HTN related events in RA studies of up to one year (Dataset 2) (Source, table 30 RA SUR)

	Cumulative Data					
	Rofecoxib					
	25 mg (N=491)		50 mg (N=458)		Naproxen (N=296)	
	n	(%)	n	(%)	n	(%)
Hypertension And Related Terms	**59**	**(12.0)**	**71**	**(15.5)**	**16**	**(5.4)**
Blood Pressure Increased	12	(2.4)	10	(2.2)	1	(0.3)
Diastolic Hypertension	0	(0.0)	2	(0.4)	0	(0.0)
Hypertension	49	(10.0)	61	(13.3)	14	(4.7)
Uncontrolled Hypertension	0	(0.0)	1	(0.2)	1	(0.3)
Discontinued Due To Hypertension And Related Terms	**6**	**(1.2)**	**4**	**(0.9)**	**1**	**(0.3)**

Table 17. HTN related events in RA extension studies (Dataset 3) (Source: Table 39 RA SUR).

	Cumulative Data					
	Rofecoxib					
	25 mg (N=823)		50 mg (N=729)		Naproxen (N=557)	
	n	(%)	n	(%)	n	(%)
Hypertension And Related Terms	**102**	**(12.4)**	**116**	**(15.9)**	**30**	**(5.4)**
Blood Pressure Increased	18	(2.2)	16	(2.2)	4	(0.7)
Diastolic Hypertension	1	(0.1)	2	(0.3)	0	(0.0)
Hypertension	84	(10.2)	99	(13.6)	25	(4.5)
Uncontrolled Hypertension	1	(0.1)	4	(0.5)	1	(0.2)
Discontinued Due To Hypertension And Related Terms	**9**	**(1.1)**	**5**	**(0.7)**	**0**	**(0.0)**

Table 18. Summary of Hypertension related events* in RA application. Source Table 13, 22 and 31, RA SUR).

	Placebo n/N %	Rofe 25 n/N %	Rofe 50 n/N %	Naproxen n/N %
Placebo controlled phase (12 weeks)	22/989 **2.2**	49/797 **6.1**	43/677 **6.4**	10/516 **1.9**
Long-term continuous (up to one-year)	-	59/491 **12.0**	71/458 **15.5**	16/296 **5.4**
Continuation and extension periods	-	102/823 **12.4**	116/729 **15.9**	30/557 **5.4**

* Includes terms such as blood pressure increased, diastolic hypertension, hypertension, uncontrolled hypertension.

Reviewer's comment: In all three datasets rofecoxib has two to three fold higher incidence of HTN-related events than naproxen. The difference with naproxen is observed early, even during the 3-month placebo-controlled phase. The rofecoxib 50 mg dose is associated with a slightly higher incidence of events than the 25 mg dose. Of note, a slightly higher number of patients had a prior history of hypertension in the rofecoxib 25 and 50 mg groups (24.5 % and 23.3% respectively) as compared to the naproxen group (21.5%). It is not clear how much this small difference in the percentage of patients with prior history of HTN contributes to the two to three fold difference in the incidence of HTN-related AE's.

7.4 CHF-related events

Table 19. Summary of CHF-related events*. (Source: Tables 13, 22 and 31, RA SUR)

	Placebo n/N	%	Rofe 25 n/N	%	Rofe 50 n/N	%	Naproxen n/N	%
Placebo controlled phase (12 weeks)	0/898	0	0/797	0	1/677	0.1	0/516	0
Long-term continuous (up to one-year)	-		0/491	0	2/458	0.4	0/296	0
Continuation and extension periods	-		1/283	0.1	4/729	0.5	0/557	0

* Includes Pulmonary edema, congestive heart failure and cardiac failure. n= patients with events. N= patients randomized.

CHF related events were more frequent in the rofecoxib 50 mg group than in the naproxen group. Findings are consistent with VIGOR.

8.0 Serious Musculoskeletal Adverse Events in the RA database.

The number of serious events related to the musculoskeletal system in the one year RA studies was higher in the rofecoxib 50 mg group compared to the naproxen group. In the one-year dataset, there were 19 events (4.1%) in the rofecoxib 50 mg group; 5 events (1.7%) in the rofecoxib 25 mg group and 9 events (1.8%) in the naproxen group. There were 9 fractures in the rofecoxib 50 mg group compared to 3 in the rofecoxib 25 mg group and none in the naproxen group.

Table 20. Fractures in the one-year RA database

	Rofecoxib 25 (N=491)	Rofecoxib 50 (N=458)	Naproxen 1000 (N=296)
Femoral	-	1	-
Hip	1	1	-
Humeral	-	3	-
Pelvic	1	-	-
Radial	0	1	-
Vertebral	1	2	-
Wrist	-	1	-

Reviewer's comment: Although this is a relatively small database, the finding of more fractures in the rofecoxib 50 mg group as compared to naproxen may reflect a clinically relevant signal. Of note in the VIGOR study (also in a population of patients with RA) there were 41 (1%) and 29 (0.7%) fractures (all sites) in the rofecoxib and naproxen groups, respectively. Bones most commonly involved were the femur (15 and 13 patients on rofecoxib and naproxen respectively) and humerus (6 and 0 patients on rofecoxib and naproxen respectively) but all areas of the skeleton were involved.

Of note, at the reviewer's request the sponsor has conducted an analysis of fractures in — placebo controlled studies of one year of longer, conducted for the evaluation of Alzheimer's disease. There were no difference in the incidence of fractures between rofecoxib 25 mg and placebo in this elderly population. This finding is somewhat reassuring, although, the RA population is known to have a higher risk for fractures than the non-RA population.

The background fracture rate for the RA population is unknown. A recent study from Finland suggests that the risk of hip fracture is increased by three fold in patients with RA, as compared with that of non-RA patients. The risk of osteoporosis may be increased because of the chronic use of steroids and because of the ongoing systemic inflammation itself. Since COX-2 is involved in regulation of bone metabolism, concerns have been raised regarding the long term bone effects of COX-2 inhibitors.

[ ]

9. Endoscopic studies.

Protocol 098 and study103 were three-month studies designed to evaluate the incidence of endoscopically diagnosed ulcers with rofecoxib 50 mg as compared with naproxen 500 mg twice daily, in patients with RA. The studies included patients infected with *Helicobacter pylori* and with potential risk factors for developing gastroduodenal ulcers on NSAIDs, such as age greater than or equal to 65 years, a prior history of a gastroduodenal PUB, the concomitant use of corticosteroids and DMARDs, and the presence of gastroduodenal erosion at baseline.

Reviewer's comment: The sponsor has presented a combined analysis of 098 and 103 and the individual study report of study 098. The individual study report of study 103 has been requested.

Review of demographic characteristics as presented by the sponsor shows that a higher number of males were randomized to naproxen (21.8%) as compared to rofecoxib 50 mg (13.7%) or placebo (18%). There were no significant differences in the age (mean 50 years), race (50% Caucasians), H Pylori status (60%), corticosteroid use (55 to 60%), alcohol use (20%), or caffeine use. The number of patients who had received NSAIDs within 30 months before enrollment was higher in the rofecoxib group (68%) and placebo (70%) as compared to the naproxen group (57%).

The primary comparison for the study was the relative incidence of gastroduodenal ulcers ≥3 mm, using the intention-to-treat life-table analysis. The sponsor states that at 12 weeks, the cumulative incidence rates of gastroduodenal ulcers ≥3 mm were significantly lower ($p<0.001$) in the rofecoxib 50-mg and placebo treatment groups, as compared to the naproxen 1000-mg treatment group. Sponsor's results are presented in the following table.

Table 21. cummulative incidence of gastroduodenal ulcers ≥3 mm in 12-week endoscopic studies in RA (Protocol 098/—). Source: Sponsor's table B74.

Treatment Group	N	Number of Patients With Incidence	Rate† (%)	95% CI for Rate (%)
Placebo	212	6	2.90	(0.61, 5.19)
Rofecoxib 50 mg	211	14	6.81	(3.36, 10.25)
Naproxen 1000 mg	210	51	25.52	(19.44, 31.59)

Between-Treatment Comparison					
Treatment	Difference of Rates (%)	95% CI for Difference (%)	Ratio of Rates	95% CI for Ratio	p-Value‡
Naproxen 1000 mg versus rofecoxib 50 mg	18.71	(11.72, 25.69)	3.75	(2.14, 6.56)	<0.001
Naproxen 1000 mg versus placebo	22.62	(16.12, 29.11)	8.80	(3.86, 20.07)	<0.001
Rofecoxib 50 mg versus placebo	3.91	(-0.22, 8.05)	2.35	(0.92, 6.00)	0.066

† Cumulative rate from the life-table analysis, it may not equal the number of events/n x 100.
‡ From the log-rank test.
CI = Confidence interval.
[P098/C]

No specific analyses of GI clinical events (i.e., symptomatic and complicated ulcers or complicated ulcers alone) were planned or performed as part of the RA efficacy program. However, potential episodes of gastroduodenal perforation, ulcers, and/or bleeding were submitted by investigators for blinded adjudication (from Protocols 068, 096, 097, and 098/103). Thirteen events were confirmed as symptomatic ulcers: two on placebo, 2 on rofecoxib 50 mg, and 9 on naproxen. Of note, there were no complicated ulcers in this relatively small database.

Reviewer's comment: The sponsor proposes adding the results of these studies to the label. The label however already includes endoscopy data compared to ibuprofen. The results of the VIGOR trial - a clinical outcome study that assessed clinically relevant data compared to naproxen - is included in the currently proposed labeling. Additional surrogate endoscopy studies do not add to the clinical outcome results in VIGOR. This reviewer does not recommend addition of the endoscopic data on naproxen to the label.

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E. Adequacy of Safety Testing

The safety evaluation of rofecoxib in this application appears adequate. Limitations of the data are discussed in section G.

F. Special populations

1. Drug-demographic interactions.

a. No new or unexpected demographic-based safety trends or issues were identified.

b. [ ]

2. Drug-drug interactions.

Differences between placebo, rofecoxib, and naproxen were generally preserved or maintained within user and nonuser subgroups for concomitant medications.

G. Summary of Critical Safety Findings and Limitations of the Data

Analysis of the data from the RA application safety database showed a trend consistent with VIGOR and ADVANTAGE: rofecoxib 25 mg and 50 mg had higher incidence of myocardial infarction, edema-related and hypertension related events than naproxen 1000 mg/day. In regards to GI safety, there were more symptomatic ulcers in the naproxen group as compared to rofecoxib and placebo. There were no complicated ulcers in this database.

The major limitations of this database are:

4. Patients at cardiovascular risk such as those with recent history of myocardial infarction and stroke and those using prophylactic low dose aspirin were not included.

5. The only active NSAID comparator used in the studies was naproxen.

6. This is a relatively small database to assess clinically meaningful outcomes.

In summary, GI and cardiovascular findings including cardiovascular thrombotic events, HTN and edema-related events are consistent with those in VIGOR and ADVANTAGE for rofecoxib compared to naproxen but do not provide comparative safety to other NSAIDs or safety information in patients using concomitant low dose ASA. The reason for the excess of MIs in the rofecoxib groups as compared to naproxen is still unclear.

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/s/

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Maria Villalba
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Lawrence Goldkind
12/21/01 03:42:47 PM
MEDICAL OFFICER

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FOOD AND DRUG ADMINISTRATION
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS -- HFD-550

Medical Officer Review

NDA 21-042 and NDA 21-052
(Rofecoxib tablets and rofecoxib oral solution)

Re: Complete response to Approvable letter for 21-042/S 007 and 21-052/S 004

Submission date (letter):	July 12, 2001
End of Review date:	November 28, 2001
Reviewer:	Maria Lourdes Villalba, M.D.
Applicant:	Merck Research Laboratories
Pharmacologic category:	NSAID (COX-2 inhibitor)
Proposed indications:	Management of acute pain, dysmenorrhea and signs and symptoms of osteoarthritis.
Dosage form and route:	Oral capsule, 12.5, 25 mg and 50 mg Oral solution 12.5 mg/5ml and 25 mg/5ml
Project Manager:	
Related reviews:	NDA 21-042/S007 (VIGOR study)
Consults:	Douglas Throckmorton, M.D. (HFD-110) Eric Bastings, M.D. (HFD- 120)

Orig NDA # 21042s007
HFD-550/Div File
HFD-550/PM/Gould
HFD-550/Statistics/SLin/QLi
HFD-550/MO/Villalba
HFD-550/TL/Goldkind
HFD-110/DDD/Thorckmorton
HFD-120/MO/EBastings

Maria Lourdes Villalba, M.D. (M.O).

Lawrence Goldkind, M.D.,
Deputy Division Director, DAIAODP

Table of Contents

Clinical Review
NDA 21-042/s007
Complete Response to Approvable Letter (4/7/01)

Executive Summary

I. Recommendations

A. Recommendation of Approvability

NDA 21-042/s007 should be Approved including labeling language that reflects available overall safety, gastrointestinal safety and cardiovascular safety in the VIOXX databases. Until prospective, randomized, adequately powered studies are performed, rofecoxib should be used with caution in patients with known cardiovascular risk, congestive heart failure and hypertension. FDA proposed labeling was sent to the applicant in October 15, 2001.

II. Summary of Clinical Findings

A. Brief Overview of the Submission

The Complete Response to the Approvable letter issued to NDA 21-042/s007 in April 7, 2001 includes the report of the **ADVANTAGE** study (a 3-month study of rofecoxib 25 mg/day and naproxen 500 mg twice daily in approximately 5600 patients with osteoarthritis -OA-) and a **Safety Update Report (SUR)** (long-term follow up of patients in the original OA program and safety data from studies not

previously submitted to the FDA). For completeness, a summary of the preliminary **safety review of the rheumatoid arthritis (RA) efficacy application** (NDA 21-042/s012) is included in this document. The RA efficacy supplement evaluated rofecoxib 25 and 50 mg doses. The active comparator was naproxen 500 mg twice daily. The current review focuses on overall safety and cardiovascular safety from all these databases.

B. Efficacy – Not applicable

C. Safety

1. The following findings apply to the ADVANTAGE and RA safety databases:

   a. Rofecoxib (25 or 50 mg) showed no overall safety advantage over naproxen 500 mg twice daily as measured by total number of deaths, serious AE's, hospitalizations, discontinuations due to AE's, and common AE's.

   b. Rofecoxib (25 or 50 mg) was associated with a nominally higher incidence of discontinuations due to HTN, edema and CHF-related events compared to naproxen 500 mg twice daily.

   c. Rofecoxib (25 mg or 50 mg) was associated with a nominally higher cardiovascular thrombotic risk (particularly an increased risk of MI) as compared to naproxen 500 mg twice daily.

   These trends (a, b and c) were observed in all studies that compared rofecoxib to naproxen: in OA and RA patients; users and non-users of low dose ASA for cardiovascular prophylaxis; short term studies (3 months) and long-term follow up datasets (up to – years). These findings are highly consistent with those in VIGOR, a large prospective outcome study that compared rofecoxib 50 mg daily to naproxen 500 mg twice daily over a median treatment period of 9 months. In VIGOR rofecoxib was associated with two fold risk of developing cardiovascular thrombotic events (p=0.001) and higher incidence of dropouts due to hypertension, edema and CHF related events compared with naproxen.

   The reason for the increased cardiovascular risk with rofecoxib 25mg and 50 mg compared to naproxen is still unknown.

2. Cardiovascular safety of rofecoxib compared to NSAIDs other than naproxen.

   There is a spectrum of COX-1/COX-2 selectivity among NSAIDs. There are no adequate long-term data comparing the cardiovascular risk of rofecoxib to traditional NSAIDs other than naproxen. Studies in the original NDA 21-042 and the SUR, were inadequate in size and duration to assess safety differences (particularly GI and CV) between either dose of rofecoxib and individual NSAIDs. Meta-analyses of small studies of different design and duration using different NSAIDs and different doses of rofecoxib are not adequate to assess whether rofecoxib has a cardiovascular safety profile similar to other NSAIDs.

3. Cardiovascular safety of rofecoxib compared to placebo.

   Data from the original NDA 21-042 and the SUR (including one-year placebo-controlled data from — studies of rofecoxib 25 mg in the prevention of Alzheimer's disease) do not provide adequate evidence that rofecoxib has a cardiovascular safety profile similar to placebo. Total cause mortality in the Alzheimer's studies was higher in rofecoxib (n=33) compared to placebo (n=20) (p=0.07, crude rate comparison). Of those, 9 and 4 were confirmed cardiovascular thrombotic deaths in the rofecoxib and placebo group respectively. Of note, although this was an elderly population (mean age 75 years), patients at high cardiovascular risk were not enrolled.

D. Dosing

Large studies included in this application used the 25 mg dose. Cardiovascular thrombotic events, hypertension, edema and congestive heart failure-related findings at the 25 mg dose were consistent in trend with the rofecoxib 50 mg dose.

E. Special Populations

1. Gender, age, race.

Effects of gender, age and race have not been addressed in this supplement. For the purpose of addressing CV or GI safety, the number of cases is small.

2. Population using low dose aspirin for cardiovascular prophylaxis.

There are no adequate long term data on concomitant use of rofecoxib in patients taking low dose aspirin (ASA) for cardiovascular prophylaxis. Limited available data from ADVANTAGE suggest that:

- the use of low dose ASA for cardiovascular prophylaxis may not eliminate the excess of cardiovascular events on rofecoxib 25 mg compared to naproxen among those patients at known cardiovascular risk.

- the use of prophylactic low dose ASA may eliminate the GI advantage of rofecoxib compared to naproxen.

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ON ORIGINAL

Clinical Review

I. Introduction and Background

Rofecoxib (VIOXX) is a non-steroidal anti-inflammatory drug (NSAID) with selective COX-2 inhibitory properties. VIOXX was approved in May 1999 for the signs and symptoms of osteoarthritis (OA) at the doses of 12.5 and 25 mg once a day, and for the management of acute pain in adults and dysmenorrhea (50 mg once a day). The use of VIOXX in children younger than 16 years of age has not been studied.

There are currently multiple NSAID products approved for the above indications. Celecoxib (CELEBREX), another COX-2 selective NSAID, is approved for OA, rheumatoid arthritis (RA) pain and for the prevention of polyps in patients with familial polyposis.

NDA 21-042/s007 was submitted in June 29, 2000. The submission included the "VIGOR" study (VIOXX Gastrointestinal Outcome Research study), studies 085 and 090 and preliminary safety data from a large study referred to as the "ADVANTAGE" study (For a detailed review of this submission the reader is referred to the 3/30/01 medical officer review). NDA 21-042/s007 proposed the ——— the NSAID template GI WARNING section of the VIOXX label. Review of the data supported some modification ——— of the GI WARNING section of the VIOXX label. Additionally, rofecoxib 50 mg showed no advantage in overall safety compared to naproxen 500 mg twice daily (deaths, serious adverse events, discontinuations due to adverse events) and raised new concerns regarding the cardiovascular safety of VIOXX: increased risk of serious cardiovascular thrombotic events with rofecoxib compared to naproxen (RR 2.37, p =0.0016).

In April 6, 2001, FDA issued an Approvable letter to supplement 007 noting that changes from VIGOR should be incorporated into the label. However, to optimally characterize the safety profile of VIOXX - particularly overall safety and cardiovascular safety – at doses indicated for chronic use in a patient population that did not specifically exclude low dose aspirin use, the division requested that the complete report of the ADVANTAGE study be submitted for review.

II. Description of Clinical Datasources

The current document includes the review of:

- The complete report of the **ADVANTAGE** study (submitted in pieces 3/30/01, 4/13/01 and 4/16/01).

- The **Safety Update report (SUR)**(submitted 7/12/01) which includes serious adverse events from the extension studies submitted in the original OA program

(studies 029, 058, 034 and 035) and from studies that had not been previously submitted to the FDA: studies [redacted]; five small studies of ≤ 6weeks duration comparing rofecoxib to other NSAIDs and studies 078, [redacted] 091 (prevention of Alzheimer's).

- Safety data from the **RA efficacy application** database (NDA 21-042/s012, submitted 2/28/01). (A summary of the Safety review is included in this document. A more detailed safety review and the Efficacy of the RA supplement are presented in a separate review).

- Additional data submitted in response to specific FDA requests for information (7/26, 7/30, 8/04, 8/17, 9/20, 20/01, 10/03, 10/05, 10/08, 11/05, 11/26/01).

III. Clinical Review Methods

The review was conducted by corroboration of sponsor's tables against full listings of adverse events as well as reviewing case report tabulations, selected case report forms and adjudication packages for cardiovascular events. Consults were obtained from the Division of Cardio-Renal (HFD-110) and Neuropharm (HFD-120) products for evaluation of specific cases where HFD-550 reviewer had concerns over accuracy of case adjudication. Published literature related to preclinical and clinical studies of COX-2 inhibitors was reviewed.

The trials appeared to be conducted in accordance with accepted ethical standards.

Evaluation of Financial Disclosure is not applicable. The main study in this application – the ADVANTAGE study – was not a covered study.

IV. Integrated Review of Efficacy – Not applicable

ADVANTAGE was a safety study. The SUR contained no efficacy data. The efficacy of the RA supplement (s012) is reviewed separately.

V. Integrated Review of Safety

A. Brief Statement of Conclusions:

1. ADVANTAGE

ADVANTAGE was a double blind, randomized, 12-week controlled study (mean duration of exposure 69 ± 30 days), comparing rofecoxib 25 mg/day to naproxen 1000 mg/day in patients with osteoarthritis. Approximately 2700 patients were randomized

into each treatment arm. Approximately 13% of patients were taking low dose aspirin for cardiovascular prophylaxis in each treatment group.

a. Rofecoxib 25 mg – the dose approved for chronic use - showed no overall safety advantage over naproxen 500 mg twice daily, as measured by the total number of deaths, serious adverse events (AE's), discontinuations due to clinical/ laboratory AE's compared to naproxen. This is somewhat striking, given the theoretical assumptions of the COX-2 hypothesis and literature publications suggesting that COX-2 selectivity would provide superior safety than non-selective NSAIDs.

Table 1. ADVANTAGE Overall Safety parameters. Percentage of patients with events.

	Rofecoxib 25 mg (N= 2785)	Naproxen 500mg bid (N=2772)
Deaths	0.2	0.1
Serious AE	2.4	2.6
Dropouts AE	13.4	13.9
Hospitalizations	1.9	1.7
Dropouts Lab AE	0.4	0.2

b. Consistent with VIGOR, there was a trend of excess in serious cardiac thrombotic events in the rofecoxib 25 mg group, compared to the naproxen group (ten and three events, respectively, as per FDA review). There were five myocardial infarction (MI), two anginal events and three sudden deaths in the rofecoxib 25 mg group and one MI and two angina (no sudden deaths) in the naproxen group. There were also two and five ischemic cerebrovascular events in the rofecoxib and naproxen groups, respectively. Two of the four CVA's on naproxen were on concomitant estrogen replacement therapy. There were no hemorrhagic strokes in the naproxen group.

c. Consistent with VIGOR twice the number of patients discontinued due to cardiovascular related adverse events (40 and 21 from the rofecoxib and naproxen groups, respectively). More patients discontinued due to HTN related events (15 and 7); edema related events (19 and 12) and laboratory adverse events (11 and 6) in the rofecoxib 25 mg group as compared to the naproxen group. There were more CHF related events (11 and 6) in the rofecoxib group as compared to the naproxen group.

d. More patients discontinued due to serious GI events in the naproxen group (142) as compared to the rofecoxib 25 mg group (113). There were 1 and 4 confirmed complicated PUBs in the rofecoxib and naproxen arm, respectively. The number of clinically relevant GI events is small but the trend was consistent with the VIGOR study.

e. Special populations: co-use of low dose ASA for cardiovascular prophylaxis

- Data suggest that the use of prophylactic ASA may not eliminate the excess of cardiovascular events on rofecoxib compared to naproxen.

The number of investigator reported serious cardiovascular adverse events for all patients (ASA users and non-users) was 23 (0.8 %) and 17 (0.6%) in the rofecoxib and naproxen groups, respectively. The number of these events in the subgroup of patients at known cardiovascular risk – as defined by concomitant use of low dose ASA – was 7/ 352 (2.0 %) and 2/ 367 (0.5 %) in the rofecoxib and naproxen group, respectively. These findings are not inconsistent with VIGOR, in which a post-hoc analysis conducted by the sponsor showed that the relative risk of developing serious cardiovascular thrombotic events for rofecoxib compared to naproxen increased from two fold in the whole population (RR:2.37, p= 0.001 for rofecoxib vs. naproxen) to five fold among those patients who might have benefited from prophylactic ASA (RR: 4.89, p= 0.01 for rofecoxib vs. naproxen).

If the cardiovascular findings in VIGOR were all explained by naproxen anti-platelet effect, a difference would not be expected between naproxen and rofecoxib in ADVANTAGE, when patients at risk in both treatment groups were already maximally protected by ASA.

- Data suggest that the use low dose aspirin – such as the dose used for cardiovascular prophylaxis - may eliminate the GI advantage of rofecoxib over naproxen.

The number of serious gastrointestinal adverse events for all patients in the trial showed a trend in favor of rofecoxib (n=7, 0.3%) as compared to naproxen (n= 21, 0.8%). In this short trial, co-use of low dose ASA increased the risk of serious GI events for rofecoxib (n=2 out of 352, 0.6%) but did not appear to increase the risk for naproxen (2 out of 367, 0.8%, unchanged). The ADVANTAGE study was too short and the number of events too small to adequately assess clinically significant GI events, particularly in the subgroup of patients using ASA, but the limited data suggest that the effects of low dose aspirin may counterbalance the COX-1 spearing effect of rofecoxib in the GI tract.

f. The findings of the ADVANTAGE study are consistent with those of the VIGOR and the RA efficacy databases. The CV findings are of concern because this is only a 12-week study, the dose of rofecoxib used in this study is 25 mg/day (half of the dose used in VIGOR), this was a different population of patients (OA instead of RA) and patients were allowed to use aspirin if indicated for cardiovascular prophylaxis. However, ADVANTAGE was not designed to address serious gastrointestinal or cardiovascular adverse events. It was too short and the number of clinically relevant adverse events was relatively small.

2. Safety Update Report.

There is no adequate evidence that rofecoxib has a cardiovascular safety profile similar to placebo or other NSAIDs.

a. Studies that compared rofecoxib to non-naproxen NSAIDs in the original NDA database and subsequently, involved too few patients to adequately assess differences in cardiovascular safety between rofecoxib and each NSAID. Studies with nabumetone were of 6 weeks duration; studies with ibuprofen were of 6 weeks to 6 months duration.; studies with diclofenac were of one year duration. Some of these studies had blinded extensions, but the actual number of patients exposed for a year or longer is very limited.

   Meta-analyses of small studies of different duration, different size and different design, involving different patient populations and different doses of rofecoxib can not adequately assess the cardiovascular safety of rofecoxib compared to individual NSAIDs.

b. Analyses of data from the Alzheimer's studies provide valuable one- year placebo-controlled data in patients age 50 years or older. However, the studies were not powered to detect differences in cardiovascular safety between rofecoxib and placebo (approximately 1500 patients randomized per treatment arm, considering the — studies together). Additionally, the studies excluded patients who had an indication for aspirin prophylaxis and those taking estrogen replacement therapy. After enrollment was complete, a protocol amendment allowed the use of low dose aspirin in those patients who might benefit from it for cardiovascular prophylaxis. A small percentage of patients were put on low dose ASA (approximately 7%).

   Although not a pre-specified endpoint, total cause mortality in the Alzheimer's studies was higher in the rofecoxib group (n=33) compared to the placebo group (n=20) (p= 0.07 for crude rate comparison). The trend of more deaths in the rofecoxib group as compared to placebo was consistent in study 091 and 078.

   Of all deaths, eight and four were confirmed cardiovascular thrombotic deaths by the CV adjudication committee in the rofecoxib 25 mg and placebo groups, respectively. This finding suggests a drug effect, rather than a lack of anti-platelet effect of rofecoxib. There were no differences in the number of serious cardiovascular potentially thrombotic events referred for adjudication in each treatment group (approximately 60 in each). A detailed review of these cases is being conducted by the Division of Cardio-renal products (HFD-110).

3. RA efficacy supplement safety database

a. Consistent with VIGOR and ADVANTAGE, rofecoxib 25 and 50 mg showed no overall safety advantage over naproxen, as measured by the total number of deaths, serious adverse events (AE's), discontinuations due to clinical and laboratory AE's and common AE's compared to naproxen.

b. Consistent with VIGOR and ADVANTAGE, rofecoxib 25 and 50 mg was associated with higher incidence of HTN, edema and CHF-related events compared to naproxen 500 mg twice daily. Incidence of HTN was consistently two to three fold higher for rofecoxib 25 and 50 mg as compared to naproxen.

c. Consistent with VIGOR and ADVANTAGE, the RA databases suggest an increased cardiovascular thrombotic risk (particularly an increased risk of MI) for rofecoxib 25 and 50 mg as compared to naproxen 500 mg twice daily. There were 4 MI in the rofecoxib 25 mg group (501 patient/years at risk), 5 MI and one sudden death in the rofecoxib 50 mg group (430 patient years at risk) and one MI in the naproxen group (406 patient years at risk).

B. Description of Patient Exposure

The ADVANTAGE study included approximately 5600 patients exposed to either rofecoxib 25 mg or naproxen 500 mg bid, with a median duration of exposure of 84 days.

The Safety Update Report includes approximately 4000 patients who received rofecoxib 25 or 50 mg of whom 1000 participated in extension studies to the original NDA OA program and 3000 participated in new studies not previously submitted to the Agency. The duration of these studies were from 4 weeks to 15 months. The size of the studies varied from a 50-patient per arm study to a 700-patient per arm study. The comparators were naproxen (approximately 500 patients), diclofenac/ misoprostol (approximately 500 patients) and ibuprofen (approximately 150 patients). The Alzheimer's studies randomized approximately 3000 patients to rofecoxib 25 mg (1500) or placebo (1500) and provide safety information for approximately 1500 patient years at risk. At the time of the submission (cut-off date for the SUR was April 2001) one of the three studies was completed (#091) one was ongoing (#078)

Approximately 1500 patients were randomized to rofecoxib 25 mg (n= 797) and 50 mg (n= 677) in 3-month placebo controlled studies. Approximately 180, 140 and 80 patients were exposed to rofecoxib 25mg, rofecoxib 50mg and naproxen 1000 mg respectively, for one year or more.

C. Summary of Critical Safety Findings and Limitations of Data

Consistent with the VIGOR study, a 8000-patient study of rofecoxib 50 mg and naproxen 1000 mg in patients with RA, the data reviewed in this submission (ADVANTAGE, SUR, RA efficacy) suggest an increased cardiovascular risk (cardiovascular thrombotic events, hypertension, edema, congestive heart failure) in patients treated with rofecoxib 25 and 50 mg as compared with naproxen 1000 mg daily. The major limitations of these databases are

1. Patients at high cardiovascular risk regardless of the use of aspirin were excluded from most of the studies.

2. The majority of studies of rofecoxib did not allow inclusion of patients using prophylactic low dose ASA. The only large study that allowed prophylactic ASA was ADVANTAGE, a study too short to assess long term effects of co-use of rofecoxib and low dose ASA. (13% of patients were on low dose ASA in each group). A few other studies that allowed inclusion of patients on low dose ASA were small and shorter than 6 weeks.

3. Naproxen was the NSAID comparator for most trials (ADVANTAGE, VIGOR, RA efficacy studies). Comparative safety data to NSAIDs other than naproxen are limited to small numbers in relatively short trials.

4. The complete comparative safety information between rofecoxib and placebo in the Alzheimer's studies has not been provided. Listings of serious adverse events and deaths and adjudication packages for cases that were referred to the CV adjudication committee have been provided for all three studies. Discontinuations due to AE were provided only study 091. Full safety reports are to be submitted.

VI. Dosing, Regimen and Administration issues

VIOXX (rofecoxib) is approved for the treatment of the signs and symptoms of OA at the doses of 12.5 and 25 mg daily and for the management of acute pain in adults and dysmenorrhea, at the dose of 50 mg once a day.

Large studies included in this application used the 25 mg dose. Hypertension, edema and congestive heart failure related findings with rofecoxib 25 mg dose were consistent in trend with the 50 mg dose.
The current label states that the use of the 50 mg dose in acute pain for more than 5 days has not been studied. However, in view of the safety issues associated with the chronic use of 50 mg (i.e. hypertension, edema, congestive heart failure and cardiovascular thrombotic events) in the VIGOR study, the label should state that the chronic use of VIOXX 50 mg dose is not recommended.

VII. Use in Special Populations

A. Effects of gender, age and race have not been addressed in this supplement. Number of events are small to adequately assess CV or GI safety in these subgroups.

B. Comments on Data Available or Needed in Other Populations: Population using low dose aspirin for cardiovascular prophylaxis.

Available data from VIGOR and the RA efficacy database suggest an increased risk of serious cardiac thrombotic events in patients with prior cardiovascular risk taking rofecoxib 25 and 50 mg as compared to naproxen 500 mg twice daily. The sponsor has speculated that the excess risk in the rofecoxib group may be due to the lack of anti-platelet effect of rofecoxib compared to naproxen and that addition of low dose ASA in high risk patients may bring down that excess cardiovascular risk.

The limited data from the ADVANTAGE study suggest that the use of low dose ASA in patients with prior cardiovascular history, might not eliminate the excess risk of serious cardiovascular events of rofecoxib compared to naproxen. Patients on low dose aspirin prophylaxis showed a trend towards more cardiovascular events than those not requiring aspirin in the rofecoxib arm (2.0% and 0.5%). This was not the case in the naproxen treated subjects (0.6% and 0.5%, respectively). This information suggests that the excess risk of CV thrombotic events on rofecoxib as compared to naproxen may be due to some mechanism other than the antiplatelet effect of naproxen. (See IV, 1, d.).

The long term effects of rofecoxib on the cardiovascular and gastrointestinal system in patients taking low dose aspirin has not been adequately assessed.

VIII. Appendices

A. Review of Individual Studies

1.0 ADVANTAGE study

1.1 Protocol design

The ADVANTAGE study (Assessment of Differences between VIOXX™ And Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness) was a randomized, double-blind, multicenter, active-controlled, 12-week study to evaluate rofecoxib 25 mg q.d. and naproxen 500 mg b.i.d. in patients with osteoarthritis (Protocols 102 and 903-0A). The use of low dose aspirin for cardiovascular prophylaxis was allowed in the study. Acetaminophen was allowed as a rescue medication in a PRN basis.

The study enrolled approximately 5,500 patients with OA of the knee, hip, hands, or spine, involving 581 investigators in the United States (protocol 102) and 19 investigators in Sweden (protocol 903-0A), from March 1999 to April 2000. Both protocols were identical as written and as implemented, except that the Swedish protocol did not enroll patients with OA of the hands. The data from both protocols were combined into one dataset, and the methods and results sections of this study report describe both protocols as a single study.

> *Reviewer's note: Although the title suggests that the protocol evaluated the effectiveness of rofecoxib, this was a safety study. The heterogeneity of the population regarding OA signal joint and the endpoints used in this trial do not allow adequate efficacy assessments. The trial was intended as a GI tolerability study. The primary hypothesis was GI tolerability but given size of the study, overall safety is as important as GI safety from the Public Health and consumer awareness point of view.*

1.2 Eligibility criteria

In general, the inclusion/exclusion criteria were similar to those used for other rofecoxib trials. The main differences between VIGOR and ADVANTAGE were:

1. ADVANTAGE included a population of patients with OA instead of RA.

2. Patients taking low dose aspirin (ASA) for cardiovascular prophylaxis were allowed in the ADVANTAGE study. Patients with recent history of MI, TIA or stroke were not explicitly excluded from the study. However, similar to VIGOR, patients on warfarin, heparin, ticlopidine and high dose aspirin were not to be included in the study.

Low dose ASA was defined for this study as doses of 81 mg/day or less. Some patients took up to 325 mg/day during the trial and they were included under the low-ASA user group.

1.3 Endpoints

The primary variable was GI tolerability, defined by the sponsor for this particular protocol as the cumulative incidence of discontinuation due to a GI AE (digestive events and abdominal pain). Other safety measures were AE incidence profiles, vital signs, and laboratory evaluations. Clinical data were collected during clinic visits (at baseline, at 6 and 12 weeks and early discontinuation) and via telephone contact (at 3 and 9 weeks of therapy). Laboratory parameters were measured at entry, week 12 and at early discontinuation visits.

Reviewer's comment: This review will focus on the overall safety, cardiovascular safety and NSAID-related AE's.

All subgroup safety analyses, including ASA user subgroups, were performed post hoc. All post hoc analyses were specified in the Data Analysis Plan (DAP), and most parameters were established prior to study unblinding, except the analysis of cardiovascular thrombotic events and the analysis of the number of perforations, ulcerations, and GI bleeds (PUBs) confirmed by adjudication and per 100 patient years.

1.4 Results.

1.4.1 Patient disposition and accounting is presented in Table 2.

Table 2. Patient disposition and accounting (Source: Sponsor's Table 20)

	Rofecoxib 25 mg qd	Naproxen 500mg bid
Patients randomized	2799	2787
Patients treated	2785	2772
Discontinued	757 (27.2)	788 (28.4)
Clinical AE	374 (13.4)	386 (13.9)
Laboratory AE	11 (0.4)	5 (0.2)
Protocol deviation	29 (1.0)	24 (0.9)
Lost to follow up	52 (1.9)	64 (2.3)
Withdrew consent	89 (3.2)	112 (4.0)
Lack of efficacy	177 (6.4)	176 (6.3)
Other	25 (0.9)	21 (0.8)

Similar number of patients discontinued from each treatment group (27-28%). The cause of discontinuation was also similar in both treatment groups. Of note, a relatively high number of patients (89 (3%) and 112 (4%) in the rofecoxib and naproxen arm, respectively) withdrew consent.

Reviewer's comment: Sponsor states that due to questionable validity, data from the 12 patients enrolled from site No. 378 were excluded from all analyses. These patients are not included in the total patient count noted above.

1.4.2 Demographic characteristics

The two treatment groups had similar demographic characteristics, arthritis treatment history at baseline and history of GI symptoms associated with NSAID use. The majority of patients were female (71.0%), and most were white (86.8%). The mean and median duration of disease were similar for both groups (approximately 69 and 84 months, respectively).

The majority of patients had used only NSAIDs prior to study entry (approximately 62% in each group). Approximately 15% had stopped NSAID treatment due to GI symptoms in the past in each arm. Patient age ranged from 36 to 97 years, with a mean age of 63 years. The most common signal joint was the knee followed by hand, spine and hip.

Reviewer's comment: The rofecoxib group included somewhat more patients with knee OA and less patients with hip OA as compared to the naproxen group. Since this is not an efficacy study, this difference is irrelevant.

1.4.3 Secondary diagnoses

The incidence of secondary diagnoses at entry were similar in both groups. Of note, 58.6% and 60.6% of patients had a diagnosis related to the cardiovascular system in the rofecoxib and naproxen groups, respectively. Approximately 45% of patients in each group had a history of hypertension.

Reviewer's comment: The percentage of patients with diagnoses related to the CV system is similar, but a 2 % difference represents 50 more patients with history of cardiovascular disease in the naproxen group and may meaningfully impact cardiovascular event rates..

1.4.4 Prior medications

The most common medications received within 30 days prior to visit 1 were acetaminophen (38%), celecoxib (19%), ibuprofen (19%) conjugated estrogenic hormones (17%) and aspirin (17%). Prior medications related to the cardiovascular system, coagulation system and hormonal replacement are presented in Tables 3, 4 & 5.