Table 37. (Cont). Serious clinical adverse events in OA studies. Data from Tables E-60 to E-67, original NDA. 6-month to 86-week OA studies.

Rofecoxib 12.5 mg/day (415)	**Rofecoxib 50 mg/day (123)**	**Diclofenac 150 mg/day (409)**
Chest pain	CHF/myocardial infarction	Myocardial infarction
Hypertension/ BP increased 2	Coronary artery occlusion	Coronary artery disease
Congestive heart failure	Weight gain/Chest pain/ CHF	Angina pectoris 2
Atrial fibrillation 2	Gastrointestinal bleeding	Chest pain
Atrial fib/neurological disorder	Pneumonia	Vascular insufficienc
Cerebrovascular accident	Cellulitis	Tachycardia
Peripheral vascular disorder		Anemia
Arterial occlusion		Metabolic encephalopathy
Deep venous thrombosis 2		Bronchitis
Aortic atherosclerosis		Pneumonia
Pancreatitis		Intestinal diverticulitis
Cholelithiasis		Esophageal ulcer
Pneumonia		Intestinal obstruction
Bacterial sepsis		Urinary tract infectio
Urinary tract infection		Urolithiasis
Polymyositis		Appendicitis
		Cellulitis
Rofecoxib 25 mg/day (435)		
Chest pain 2		**Nabumetone 1500 mg/day (92)**
Coronary vasospasm		Atrial fibrillation/CHF
Angina pectoris		Chest pain/ CHF
Coronary artery disease		
Congestive heart failure		
Deep venous thrombosis		
Paralytic ileus		
Peristaltic motion disturbance		
Abdominal pain		
Infectious gastroenteritis		
Intestinal diverticulitis		
Gastric ulcer / GI obstruc		
Hemorrhagic peptic ulcer		
Lower GI hemorrhage		
Pancreatitis		
Asthma		
Pneumonia		
Abscess		
Osteonecrosis		
Renal colic		
Urolithiasis (2)		

(n)= number of patients randomized to the studies. * Includes study 034 & 035 (second six month) and extension 34C, 29-10/20/30 and 058-10

c) Adverse events with incidence higher for rofecoxib vs. placebo in 6 week studies (Appendix 15)

In 6 week studies adverse events with incidence higher than placebo were hypertension, edema, some GI adverse experiences (nausea and heartburn), oral ulcers, and depression.

In six-month and 6-month to 86-week studies, the incidences of hypertension and edema were similar between rofecoxib at the doses of 12.5 and 25 mg QD and the NSAID comparators. Rofecoxib 50-mg QD showed higher incidence of renal-related adverse events than the 12.5 and 25 mg QD doses. In the six-month studies, the most striking difference was in the incidence of hypertension (4.5 %, 5.6 %, 10.3% and 4.6 % for rofecoxib 12.5, 25, 50 mg QD and ibuprofen respectively) and edema (4.1 %, 4.2 %, 6.6% and 1.3 % for rofecoxib 12.5, 25, 50 mg QD and ibuprofen respectively).

> ***Reviewer's comment: in 6 month studies the incidence of hypertension on the rofecoxib 50 mg QD group was double than in the 12.5 and 25 mg groups and than NSAID comparators.***

Other adverse events more common in rofecoxib than in the placebo group were nausea, epigastric discomfort and oral ulcers.

d) Patient discontinuation due to clinical adverse experiences (Appendix 16)

Discontinuation due to clinical AE in the 6-week OA trials were mostly due to "body as a whole/site unspecified" adverse experience. This category included edema, peripheral edema, fluid retention, lower extremity edema, and upper extremity edema. Incidence of this category of AE was evenly distributed among rofecoxib 12.5 to 50 mg QD and active comparators, but was higher in the rofecoxib 125 mg group. The second most common cause of discontinuation was adverse events related to the digestive system. Patient discontinuation on rofecoxib was numerically similar to ibuprofen and higher than placebo. Of note, abdominal pain was not included under "digestive system" but included under the category of "body as a whole".

In 6-month studies the most common cause of discontinuation was due to AE related to the digestive system. Rofecoxib 50 mg had a similar incidence of discontinuation due to digestive AE compared to ibuprofen 2400 mg/d and diclofenac (4.7%, 4.8% and 4.4% respectively) and was numerically higher than rofecoxib 12.5 and 25 mg (3.7% and 2.8 % respectively). Placebo patients had only four-month exposure and no direct comparisons can be made (incidence in placebo group was 1.9%). The incidence of discontinuation due to cardiovascular adverse events for rofecoxib 50 mg was similar to ibuprofen and diclofenac (1.6 %, 1.3 % and 2.0 % respectively) and was numerically higher than rofecoxib 12.5 and 25 mg (1.0 % and 0.9 % respectively).

2.6.1.2. Laboratory adverse experiences

Evaluation of laboratory data was performed by review of shifts in mean laboratory values, the incidence of laboratory adverse events, the percentage of patients exceeding the predefined limits of change from baseline and the incidence of discontinuations due to laboratory adverse events among patients in the controlled osteoarthritis trials.

There were no substantial shifts in mean laboratory values in sodium, potassium, BUN, creatinine, glucose, hemoglobin and hematocrit among patients in OA trials (however, mean changes do not reflect individual variations).

Compared with the values at randomization (after NSAID washout), very slight changes in mean serum creatinine were noted after 6 weeks of study therapy (-0.01 mg/dL in the placebo group versus -0.01, 0.02, 0.04. 0.04, 0.11, 0.02, and 0.06 mg/dL in the groups receiving 5, 12.5, 25, 50, 125 mg rofecoxib, ibuprofen, and nabumetone, respectively) and after 6 months of study therapy (-0.02 mm Hg in the placebo group versus 0.00, 0.03, 0.06, 0.02, and 0.02 in the groups receiving 12.5, 25, 50 mg MK-0966, diclofenac, and ibuprofen, respectively).

Mean changes in serum sodium and serum potassium were assessed for the 6-Week, 6-Month, and 1-Year Studies. Compared with the values at randomization (after NSAID washout), the mean change in serum sodium did not exceed 1% of the baseline value for any treatment group in any study. Compared with the values at randomization (after NSAID washout), the mean change in serum potassium did not exceed 5% of the baseline value for any treatment group in any study.

Table 38. Select laboratory Adverse Events in 6-week OA studies

	Placebo N= 622 n (%)	Rofecoxib				Ibuprofen 800 mg TID N=466 n (%)
		12.5 mg/d QD N=867 n (%)	25 mg/d QD N=942 n (%)	50 mg/d QD N=96 n (%)	125 mg/d QD N=74 n (%)	
↑BUN*	1	7 (0.8)	6 (0.6)	0	-	3 (0.6)
↑Creatinine	0	8 (0.9)	6 (0.6)	0	0	3 (0.6)
↑K	0	2	2	3 (3.0)	0	0
Hyperglycemia	3 (0.5)	7 (0.8)	4	1	0	5 (1.0)
Proteinuria	3 (0.5)	9 (1.0)	1	1 (1.0)	1	4 (0.8)
Hematuria	0	2	0	1 (1.0)	0	0
↑ALT	2	18 (2.0)	16 (1.7)	1 (1.0)	4 (5.4)	6 (1.3)
↑AST	4	16 (1.8)	13 (1.3)	1 (1.0)	4 (5.4)	(1.3)
↑Alk Phos	0	10 (1.2)	2	0	2 (1.5)	2

N: patients with available safety data. n: number of events. Percentage is noted for events in ≥ 0.5% of patients. Includes Phase II and III 6-week studies. * BUN was not measured in study 010. Nabumetone was not included in the table.

In 6-week studies, a higher number of patients had increased BUN, increased creatinine, hyperkalemia, hyperuricemia, increased AST and ALT, proteinuria and decreased hemoglobin or hematocrit in the rofecoxib groups vs. the placebo group (Table 38).

In 6-month studies, relevant laboratory adverse events were increased BUN and creatinine, ALT and AST, hyperkalemia, hyperuricemia and proteinuria. There was a trend suggestive of a dose-response curve for rofecoxib (Table 39). The incidence of hyperglycemia seemed to be evenly distributed .

The incidence of rofecoxib laboratory adverse events was generally similar to the active comparators (ibuprofen and diclofenac) except for liver function tests abnormalities that were higher in the diclofenac group. Since the placebo group was only exposed for 4 months, no direct comparisons can be made to placebo.

Table 39. Select laboratory Adverse Events in 6-month OA studies

	Placebo* N=363 n (%)	Rofecoxib 12.5 mg/d QD N=486 n (%)	Rofecoxib 25 mg/d QD N=868 n (%)	Rofecoxib 50 mg/d QD N=372 n (%)	Ibuprofen 800 mg TID (N=371) n (%)	Diclofenac 50 mg TID (N=496) n (%)
↑BUN	2 (0.6)	4 (0.8)	17 (2.0)	12 (3.2)	10 (2.7)	10 (2.0)
↑Creatinine	1	4 (0.8)	17 (2.0)	15 (4.0)	6 (1.6)	3 (0.6)
↑K	0	0	10 (1.2)	5 (1.3)	4 (1.1)	3 (0.6)
Proteinuria	2 (0.6)	10 (2.0)	17 (2.0)	6 (1.6)	4 (1.1)	9 (1.8)
Hematuria	5	3 (0.6)	6 (0.7)	1	1	1
Hyperglycemia	5 (1.3)	4 (0.8)	8 (1.0)	6 (1.6)	6 (1.6)	4 (0.7)
Hyperuricemia	1	1	6 (0.7)	2	1	2
↓Bicarbonate**	1/363		1/385	1/372	1/371	
↑ALT	11 (3.0)	12 (2.5)	29 (3.3)	9 (2.4)	13 (3.5)	59 (11.9)
↑AST	13 (3.6)	13 (2.7)	26 (3.1)	10 (2.6)	10 (2.7)	44 (8.9)
↑Alk Phos	4 (1.1)	8 (1.6)	19 (2.1)	5 (1.6)	5 (1.3)	8 (2.2)
↓Hgb	3 (0.8)	2 (0.6)	15 (1.7)	25 (6.7)	16 (4.3)	12 (2.4)
↓Htc	9 (2.5)	3 (0.6)	28 (3.2)	31 (8.4)	28 (7.5)	15 (3.0)
↓ Leukocytes	7 (1.9)	3 (0.6)	12 (1.4)	7 (1.9)	5 (1.3)	2
↓ Platelets	5 (1.4)	3 (0.6)	5 (0.6)	4 (1.1)		2

N= Number of patients with available safety data. n= number of events. * Placebo group had only 4 months of exposure. ** Bicarbonate was measured only in study 044 and 045. Percentages are only listed for events with incidence ≥ 0.5% Source Table E-87 of NDA., Study 044, 045, first 6 months of 034 and 035)

A list of percentage of patients exceeding predefined limits of change is presented in Appendix 17. Analysis of these data lead to similar conclusions: there is a higher number of patients with increased BUN, creatinine, hyperkalemia and proteinuria among patients in the rofecoxib 50 mg dose as compared to the 12.5 and 25 mg dose and to the active comparators. The 50 mg dose had also more patients who exceeded predefined limits for hyperuricemia and hypocalcemia in 6-month studies. In regards of hematologic laboratory adverse events, there is a higher number of patients with decreased hemoglobin and hematocrit among rofecoxib patients when compared with placebo in the 6-month studies; this effect is more marked with the 50 mg dose. (See Hematology

review) The incidence of decreased WBC was numerically higher with all rofecoxib groups than with placebo, but the placebo rate itself was relatively high (see Appendix 17).

Few patients discontinued due to laboratory adverse events.
There were no serious laboratory adverse events.

120-day Safety Update Report

Safety Update Report (SUR) data refer to data derived from patient visits that occurred during the SUR-reporting period, 1/4/98 to 4/9/98. This report provides additional safety data from:

1. The Long-Term Exposure Osteoarthritis Studies (termed 6-Month-to-86-Week Studies in the Application) (818 patients). Some of these patients have completed 2 years of treatment.
2. Extension data for the Elderly OA Study (Protocol 058). Duration of exposure to rofecoxib now exceeds 1 year for some patients in this study.
3. Studies that were completed during the SUR: Post-Dental Surgery Pain Study (Protocol 084, 223 patients) and Bioequivalence Study (Protocol 087, 25 subjects).
4. Safety data for Part I of the Rheumatoid Arthritis Dose-Ranging Study (Protocol 068, 658 patients).

In general SUR safety data are consistent with the safety profile originally reported. There were no findings on new clinically important adverse experiences with this longer duration of exposure. No deaths occurred during the SUR.

Combined data from the base studies and extensions was called "Cumulative data". Long-term exposure data in OA studies and study 058-extension showed a higher incidence of adverse experiences for the Cumulative than for the original Application data. This finding was consistent with expectations based upon the increased duration of exposure to the study drug. The clinical pharmacology and analgesia studies showed a similar adverse experience profile than in the original application data. These studies were of short duration and generally conducted in healthy subjects.

Serious nonfatal adverse events were of similar nature than the ones seen in the original Application. Again the most frequent nonfatal serious adverse experiences occurred in the cardiovascular system. Most patients had risk factors for cardiovascular disease.

2.6.2. SAFETY IN RHEUMATOID ARTHRITIS STUDIES

Data from one phase II study in RA (017) and its extension were submitted to the original NDA 21-042.

1. Study 017 (Pilot study in RA.

This was a six-week double blind, multicenter, placebo-controlled parallel study to assess the safety and preliminarily evaluate efficacy of rofecoxib in patients with R.A. A total of 137 patients were randomized to receive rofecoxib 125 mg/day, 175 mg/day or placebo (41, 28 and 68 patients respectively). Efficacy data will not be analyzed in this review, although it is worth mentioning that 18 (26.5%) of the patients randomized to placebo and only 3 (4.3%) of the patients randomized to rofecoxib, discontinued due to lack of efficacy.

The safety profile of rofecoxib in patients with RA was similar to the one seen in patients with OA. However, at these higher doses, there was a higher incidence of edema/fluid retention and related adverse events: changes in mean body weight (mean maximum change 0.9 kg with Rofecoxib compared with -0.1 kg with placebo); increased systolic blood pressure (mean maximal change 5.90 and -0.73 mm Hg for rofecoxib and placebo, respectively); increased diastolic blood pressure and a small increase in mean serum creatinine (0.10 mg/dl on rofecoxib compared with 0.009 mg/dl with placebo).

The total incidence of edema-related adverse experiences was significantly greater in the rofecoxib group (13.0 and 2.9% in the rofecoxib and placebo treatment groups, respectively ($p<0.05$). These adverse experiences were mild or moderate in severity, with the majority determined by the investigators to be possibly related to study medication. Of the 11 patients reporting edema-related adverse experiences, none had either a history of edema or edema on the physical examination at the Screening Visit. In addition to edema, AN 63 had adverse experiences of weight gain, dyspnea, and increased serum creatinine.

There were more patients with cardiovascular AEs in the rofecoxib 175 mg group than in the placebo group. (Table 9). The number of patients enrolled in this study was small and no conclusions can be drawn from these data.

Table 40. Patients with CV adverse events in study 017 (six-week in RA).

Listing of Patients With Cardiovascular Adverse Experiences

AN	Age	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Relationship	Action
MK-0966 125 mg							
11	61	43	T-wave increased	1 day	N/A	Possibly	PRx continued
41	73	8	Acute myocardial infarction	7 days	Severe	Definitely not	Discontinued PRx
MK-0966 175 mg							
52	79	16	Hypertension	14 days	Mild	Probably not	PRx continued
53	64	43	Left atrial enlargement	1 day	Mild	Definitely not	PRx continued
		43	Nonspecific S-T changes	1 day	Mild	Definitely not	PRx continued
92	56	43	Hypertension	1.5 years	Mild	Probably not	PRx continued
121	60	9	Peripheral vascular disorder	14 days	Moderate	Possibly	PRx continued
		23		28 days	Mild	Possibly	PRx continued
186	24	47	Sinus bradycardia	1 day	N/A	Probably not	PRx continued
Placebo*							
62	37	15	Irregular heartbeat	14 days	Mild	Probably not	PRx continued
159	61	44	Blood pressure increased	3 days	Mild	Definitely not	PRx continued

* Pooled 125 and 175 mg-image treatment groups.
N/A = Not applicable, intensity is not defined for ECG adverse experiences.

A decrease in hemoglobin (mean maximal change 0.74 and 0.25 g/dL for the rofecoxib and placebo treatment groups, respectively) occurred at the first treatment evaluation (1 week) and remained fairly constant during the 6-week treatment period.

The incidence of digestive system adverse experiences was 33.3 and 22.1% for the rofecoxib and placebo groups, respectively. These differences were not statistically significant. In this study, there were no occurrences of upper GI perforation, ulceration or bleeding.

The incidence of oral mucosa adverse experiences (oral ulcer, aphthous stomatitis, and tongue lesion) was 4.3 and 0.0% in the rofecoxib and placebo treatment groups, respectively. Most of them resolved while on continued therapy.

2. Study 017c, extension studies in RA.

Design: Study 017c was a double-blind, active comparator-controlled study to assess safety and tolerability and preliminarily evaluate the efficacy of rofecoxib in the treatment of patients with Rheumatoid Arthritis for **16 weeks** (first extension) and **30 weeks** (second extension).

Treatment: 60 patients received rofecoxib 125 mg QD; 13 patients received ibuprofen 800 mg TID.

Safety results: During the First Extension, the total incidence of adverse experiences of hypertension and blood pressure increased was 11.7% (7/60) and 0.0% (0/13) in the rofecoxib and ibuprofen groups, respectively. Of these seven patients, four did not have a previous history of HTN and four discontinued treatment due to the adverse event. At the initial measurement in the first extension (Week 8), patients treated with rofecoxib showed an increase in mean body weight of approximately 0.5 kg compared with baseline.
Edema related adverse experiences occurred in 16.7% of patients in the rofecoxib group. No episodes of edema were seen in the ibuprofen group.

In the Second Extension, there were no serious adverse experiences. Seven of the 9 patients on rofecoxib showed nonserious clinical adverse experiences. No laboratory adverse experiences were reported.

3. Study 068 (120-day Safety Update).
This was a randomized, double blind, multi-center two part dose ranging study of 60 patients with RA who received placebo, rofecoxib 25 or 50 mg QD. The first part (8-week data) was submitted to the Safety Update. The second part (additional 44 weeks) is undergoing. The nature of the serious adverse events appears to be similar to the events seen in OA patients who received the same doses. The only death that occurred during this study has already been reported in the original NDA (although at that time the study was still blind).

7. Safety by body system

7.1. OVERVIEW OF HEMATOLOGY SAFETY

For a more detailed review the reader is referred to Dr. Ann Farrell's review (Hematology Consultant).

7.1.1.Platelet function.

Conventional NSAIDs are dual COX-1 and COX-2 inhibitors. Inhibition of COX-1 is associated with inhibition of platelet thromboxane A2 (TXA2) resulting in impairment of platelet aggregation and hemostasis. Platelets constitutively express COX-1 but lack nuclear structure and are unable to upregulate COX-2. In this NDA the effect of rofecoxib on platelet function was evaluated by measuring platelet aggregation, bleeding time and by prostaglandin production assays.

a) COX-1 activity was measured by decrease in TXB2 levels.
TXA2 is a product of COX-1 activity. It is relatively unstable and undergoes hydrolysis to TXB2, and inactive metabolite. TXB2 may be measured in serum "ex vivo" or, "in vivo" indirectly, by measuring urinary metabolites (one of the major ones is 11-dehydrothromboxane B2). A selective COX-2 inhibitor should not affect the serum and urinary levels of the thromboxanes.

b) COX-2 activity was measured by increase in LPS-induced PGE2.
Lipopolysaccharide-induced prostaglandin E2 (LPS-induced PGE2) is produced by the COX-2 isoform. Serum levels may provide an assessment of COX-2 "ex vivo". Urine metabolites are an indirect measure of systemic biosynthesis and metabolism of COX-2 products.

In Clinical Pharmacology studies, rofecoxib at single doses up to 1000 mg and daily doses up to 350 mg QD for up to 12 days duration did not appear to affect platelet aggregation and bleeding time. Comparators (naproxen 550 mg BID, ibuprofen 800 mg TID, diclofenac 50 mg TID, meloxicam 15 mg QD) significantly reduced TXB2 levels, platelet aggregation and prolonged bleeding time. Rofecoxib demonstrated significant COX-2 inhibition without substantial inhibition of COX-1 activity. There was a significant variability for individual patient's serum TXB2 at various doses. Some patients experienced a decrease in serum TXB2 levels up to a 60%, but this observed decrease did not appear to be does dependent. There was also great variability among patients on placebo. (for more details see Dr. Ann Farrel's review).

7.1.2. Hematologic effects in OA clinical studies.

There was a higher incidence of patients with decreased hemoglobin and hematocrit among rofecoxib patients as compared to placebo. This effect appears to be dose related. (Table 41).

Table 41. Patients exceeding predefined limits of change from baseline for Hemoglobin and Hematocrit. (Source, original NDA).

Laboratory Test	Predefined Limit of Change From Baseline	Treatment	Number*/Total† (%)		
			6-Week Studies‡	6-Month Studies‖	6-Month-to-86-Week Studies Plus Protocols 029-10 and 058-10
Hematocrit (%)	Decrease ≥6.0% (absolute decrease)	Placebo	8/397 (2.0)	4/346 (1.2)	NA
		MK-0966 5 mg	5/142 (3.5)	NA	NA
		MK-0966 12.5 mg	11/710 (1.5)	3/485 (0.6)	26/540 (4.8)
		MK-0966 25 mg	23/720 (3.2)	24/858 (2.8)	40/539 (7.4)
		MK-0966 50 mg	11/93 (11.8)	37/360 (10.3)	24/119 (20.2)
		MK-0966 125 mg	8/72 (11.1)	NA	NA
		Ibuprofen 2400 mg	27/464 (5.8)	38/353 (10.8)	NA
		Diclofenac 150 mg	NA	18/495 (3.6)	39/434 (9.0)
		Nabumetone 1500 mg	0/114 (0.0)	NA	1/85 (1.2)
Hemoglobin (gm/dL)	Decrease ≥2.0 gm/dL	Placebo	2/398 (0.5)	5/346 (1.4)	NA
		MK-0966 5 mg	3/142 (2.1)	NA	NA
		MK-0966 12.5 mg	2/711 (0.3)	8/485 (1.6)	12/540 (2.2)
		MK-0966 25 mg	8/720 (1.1)	16/858 (1.9)	28/540 (5.2)
		MK-0966 50 mg	1/93 (1.1)	23/360 (6.4)	12/119 (10.1)
		MK-0966 125 mg	2/73 (2.7)	NA	NA
		Ibuprofen 2400 mg	14/464 (3.0)	25/353 (7.1)	NA
		Diclofenac 150 mg	NA	29/495 (5.9)	31/434 (7.1)
		Nabumetone 1500 mg	0/114 (0.0)	NA	1/85 (1.2)

The cause of the decreased hemoglobin and hematocrit is not completely clear. One GI study (Study 050) showed that occult GI blood loss over a 4-week interval was similar in patients treated with rofecoxib 25 and 50 mg daily compared to placebo. However, it is possible that this study did not capture occult GI loss that could happen over longer periods of time. There was no evidence of bone marrow effect. The data indicates that the use of rofecoxib was associated with fluid retention. Therfore it is possible that the decrease in hemoglobin and hematocrit were secondary to hemodilution.

7.2. UPPER G.I. SAFETY – OVERVIEW AND SPECIAL STUDIES

The central hypothesis of the rofecoxib development program was that rofecoxib would be safer than non-selective COX-2 inhibitors to the GI mucosa . Three studies in healthy subjects (041, 050, 009) and two endoscopic studies in patients with OA (044, 045) were performed to evaluate the effects of rofecoxib in the GI mucosa. A pooled analysis of GI adverse events in all of ≥ 6-week studies was also performed (069). For a more detailed review, the reader is encouraged to read Dr. Goldkind's (GI consultant) review. Appendix 18 shows all studies conducted for evaluation of GI safety in this NDA.

7.2.1. Overview. Deaths, serious adverse events and events requiring withdrawal.

There were no deaths related to upper GI adverse events in the entire database.

In 6-week studies, the only serious adverse event due to GI bleeding was in a patient on rofecoxib 125 mg QD (AN 1140). In 6-month studies, four serious GI related events were felt by the investigator to be drug related (all among patients on rofecoxib). Reports included one intestinal obstruction (AN 7507) and one "colitis" (AN 8292) in the rofecoxib 12.5 mg; one GI bleeding due to a duodenal ulcer (AN 5324) and one gastric ulcer complicated with GI obstruction (AN 5605) in the rofecoxib 25 mg group. No serious GI adverse events were considered by the investigator to be related to diclofenac. There were no serious GI adverse events in the ibuprofen group. In 6-month to 86-week studies, four patients (three on rofecoxib: AN 2281(infectious gastroenteritis), AN 7985 and AN 4300 (two GI bleedings), and one on diclofenac AN 7993 (esophageal ulcer) had serious GI adverse events considered drug related. No serious events were felt by the investigator to be related to ibuprofen or nabumetone.

AE related to the digestive system were the most common cause of discontinuation in 6-month studies. Rofecoxib 50 mg had a similar incidence of discontinuation due to digestive AE compared to ibuprofen 2400 mg/d and diclofenac (4.7%, 4.8% and 4.4% respectively) and was numerically higher than rofecoxib 12.5 and 25 mg (3.7% and 2.8 % respectively). Placebo patients had only four-month exposure and no direct comparisons can be made (incidence in placebo group was 1.9%).

7.2.2. Studies 044, 045 and 044C.

Study characteristics: Studies 044 (US) and 045 (Multinational) were identical, multicenter, randomized, double blind, placebo and active-comparator (ibuprofen) controlled 12 week studies, with a 12 week extension, to assess the incidence of endoscopic ulcerations in patients with osteoarthritis. Study 044C was the pooled analysis of 044 and 045.

Demographics: 742 patients were enrolled in study 044 and 775 in study 045. The age and gender distribution and the percentage of patients with endoscopic erosions at baseline were similar in both studies. Protocol 044 had more patients with a history of

PUB and a history of prior NSAID use. Protocol 045 had a higher percentage of patients with *H. pylori* infection at baseline.

Design: After a washout period from NSAIDs and gastroprotective agents, patients were randomized to placebo, rofecoxib 25 or 50 mg QD or ibuprofen 800 mg TID for 12 weeks. Upper GI endoscopies were performed at entry, 6 weeks, 12 weeks and at the end of the study. The primary analysis was the incidence of GI ulcerations of ≥ 3 mm size at 12 weeks.

After 16 weeks, 95% of placebo and 5 % of patients in other treatment groups were discontinued in a blinded fashion using Discontinuation Schedule envelopes that revealed only whether the patient should either continue or undergo scheduled discontinuation. If a patient had to discontinue before reaching a scheduled discontinuation at either Week 16 or 24, the investigator was expected to make every effort to perform an upper GI endoscopy to determine mucosal status as soon as possible. If an ulcer was detected during routine endoscopy, the patient was referred for appropriate follow-up.

Statistical analysis plan: Comparability criteria for the comparison of rofecoxib 25 mg to placebo were prespecified for a combined analysis of the 2 studies, based on the assumption that the GD ulcer incidence rate of the placebo and ibuprofen groups would be approximately 2.5 and 15 % respectively. The applicant considered that the treatment would be comparable to placebo if the difference of rates between rofecoxib 25 mg and placebo was LESS than 4 percentage points. A difference of ≥ 4% was considered to be clinically meaningful.

Table 42. Study 044 and 045 randomization and patient accounting

	Study 044				Study 045			
	Placebo	Rfx 25 mg QD	Rfx 50 mg QD	IBU 800 mg TID	Placebo	Rfx 25 mg QD	Rfx 50 mg QD	IBU 800 mg TID
Patients randomized (n)	177	195	186	184	194	195	193	193
Excluded from ITT analysis endoscopic endpoints	19	9	8	17	12	8	11	6
Discontinued (% n)	32.8	30.2	34.4	60.9	21.7	29.2	34.2	58.6
Lack of efficacy	9.0	3.1	2.2	4.9	3.6	3.1	1.6	2.6
Adverse events	7.9	10.3	12.3	14.7	3.6	5.6	10.9	9.8
Due to study endpoint	5.6	5.6	10.2	29.3	2.6	7.7	9.8	37.8
Pt withdrew consent	4.0	6.7	7.5	10.0	6.7	7.7	8.3	5.2
Protocol deviation	5.1	1.5	2.2	4.3	3.1	2.6	2.1	2.6
Lost to follow up	0.6	1.5	2.2	1.6	1.6	1.0	1.0	0

Reviewer's comment: The discontinuation at 12 weeks was higher in patients on ibuprofen than in any other treatment group (near 60 % compared to 22 - 34 % in other groups). This was due in part to the fact that patients who developed

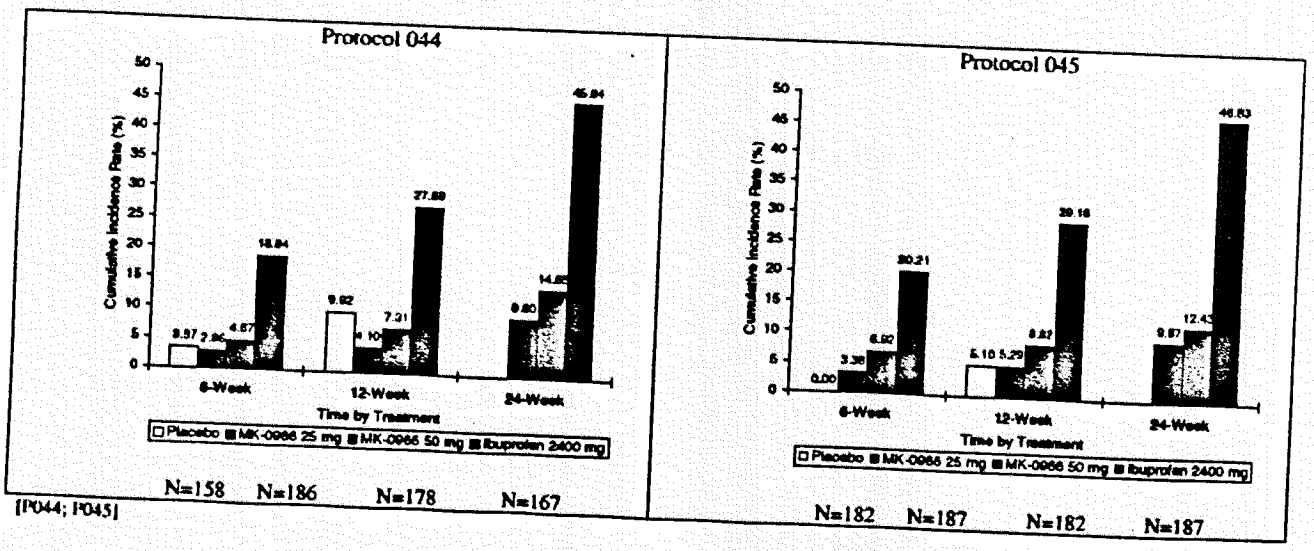
asymptomatic endoscopic ulcerations were withdrawn from the study. (Fifteen patients who developed erosions were also withdrawn from the study). It is known that many endoscopic ulcerations are asymptomatic and may come and go without complication. While it is understandable that the physician would feel uncomfortable continuing the patient in the study, the early dropout of patients who could have finished the study without developing symptomatic ulcers may have had an impact in the final results, particularly the survival analyses of GI adverse events.

In both studies the rate of discontinuation due to clinical adverse events in the rofecoxib 50 mg QD group was similar to ibuprofen and higher than the 12.5 and 25 mg QD groups.

The primary analysis was an ITT analysis of endoscopic ulcers at 12 weeks. The applicant used a modified ITT approach. Patients who lacked "treatment phase" endoscopy were excluded from the analyses. Fifty three of 742 patients were excluded from the "ITT" analysis in study 044 and 37 of 775 patients were excluded from study 045. The most frequent reason for these patients not to have a follow up endoscopy was "patient withdrew consent". 6.1 % and 7.0 % of patients withdrew consent, from protocol 044 and 045 respectively (these numbers appear to be unusually high). A random evaluation of 25 of these patients suggested that two of the 25 had actually withdrawn the consent due to adverse events and one patient had discontinued because of lack of efficacy.

Results of these studies as analyzed by Merck are summarized in Figure 4.

Figure 1. Studies 044 and 045. Life table cumulative incidence rate of gastroduodenal ulcers ≥ 3 mm (ITT)



[P044; P045]

Reviewer's comment: Rofecoxib was clearly associated with fewer endoscopically defined ulcers than ibuprofen. However rofecoxib was not the same as placebo. There was evidence of a dose-response for endoscopic ulcers with rofecoxib. The placebo rate of 9.9 % in study 044 was surprisingly high compared to a rate of 3.4 % in study 045. This difference is not negligible; the statistical analysis plan had stated that a difference of ≥4% points in the incidence of endoscopic ulcers would be considered significant. The comparability bound of 4% had not been pre-defined in agreement with the FDA. These two studies can not be simply pooled for analysis. Additionally, For a detailed review, see Dr. Goldkind (GI) and Dr. Li's (Statistical) reviews.

7.2.3. Study 069

Study 069 was a "pre-defined" pooled analysis of GI adverse events in all OA trials of 6 weeks or more. GI adverse events were divided into two categories: PUB's and NSAID-like GI events.

Reviewer's comment : FDA reviewers have several concerns surrounding the analyses and interpretation of this study. Study 069 pooled data of approximately 3300 patients from studies with different duration (four six-week studies [029, 033, 040, 058], two endoscopic 6-month studies [044 and 045[and two one-year studies [034 and 035]), and with different doses of rofecoxib (12.5, 25 and 50 mg QD) despite the fact that there was evidence of an adverse event dose-response, particularly for the 50 mg dose when compared to the 12.5 and 25 mg doses. The bulk of the patients (approximately 2900) were exposed to 12.5 and 25 mg doses from 6 months to one year (some of them, up to 86 weeks). Only approximately 450 patients were exposed to 50 mg QD for up to 6 months. The three NSAID comparators (ibuprofen, diclofenac and nabumetone) were pooled under the NSAID category. Pooling these data may not be appropriate because the incidence of GI adverse events among the comparators was not homogeneous (it was higher in the ibuprofen than in the diclofenac and nabumetone groups) and there was a higher number of patients exposed to ibuprofen and diclofenac than to nabumetone. It is also questionable that one of the 6-week OA studies (010) was not included into the analysis. This study had one patient with a complicated GI bleeding in the rofecoxib 125 mg group. The reader is referred to Dr. Goldkind and Li's reviews.

As noted by the GI reviewer, GI adverse events causing withdrawal and PUB data are consistent with a somewhat lesser incidence of GI adverse events for rofecoxib 25 mg, compared to the NSAID comparators. The degree of differentiation between other NSAIDs and rofecoxib in terms of clinically relevant endpoints cannot be well quantitated based on the data available from the GI studies in this submission. A large simple trial with clinical endpoints using appropriate clinical doses of rofecoxib and comparators will answer this question better than is currently possible.

7.3. REVIEW OF HEPATOBILIARY SAFETY

7.3.1. Rofecoxib pharmacokinetics in hepatic impairment

A pharmacokinetic study in mild (Child-Pugh Class I) hepatic insufficiency patients indicated that rofecoxib AUC was similar between these patients and healthy subjects. In patients with moderate (Child-Pugh Class II) hepatic insufficiency, a trend towards higher AUC of rofecoxib was observed. Patients with severe hepatic insufficiency were not studied.

7.3.2. Liver function tests in controlled OA trials (Appendix 20).

In 6-week studies, the incidence of increased liver function tests (LFT's) was higher in the active treatment groups than in the placebo group.

In 6-month studies there were numerically more patients with increased ALT and AST in the diclofenac group compared with all other active treatments. GGTP, another marker of liver damage (measured in some patients), was also increased, up to 5%, 7% and 3.3% among patients on rofecoxib 25 mg/d, ibuprofen, and diclofenac respectively.

In ≥ 6-month studies the number of patients with elevated AST and ALT was three times higher in the diclofenac group than in the rofecoxib groups. In these studies, five patients were discontinued from rofecoxib (one in the 12.5 mg group and four in the rofecoxib 25 mg) as compared to 24 patients in the diclofenac group.

Patients with LFT elevations >3 times the upper limit of normal in controlled OA studies

Table 43. Patients with ALT or AST elevations > 3 times the upper limit of normal in all osteoarthritis studies.

	Placebo	Rofecoxib				Comparators		
		12.5 mg	25 mg	50 mg	125 mg	Diclofenac 150 mg/d	Ibuprofen 2400 mg/d	Nabumetone 1500 mg/d
Patients with AST a/o ALT elevation >3 ULN	1 / 783	10 / 1215	17 / 1614	9 / 476	3 / 74	45 / 498	2 / 847	1 / 115
Percentage	0.1	0.8	1.1	1.9	4.1	9.0	0.2	0.9

Considering all osteoarthritis trials, rofecoxib at the doses of 50 and 125 mg QD had a numerically higher incidence of LFT >3 ULN compared to the 12.5 and 25 mg doses and to ibuprofen. There was a clear dose-response but the highest dose of rofecoxib still showed fewer cases of LFT elevations than diclofenac.

Most of the LFT elevations at the dose of 12.5 and 25 mg QD resolved to <2 times normal while the patient remained on study therapy (6 of 10 patients and 7 of 17 patients with elevations respectively). This was also true of the events in the ibuprofen and

nabumetone groups while in the diclofenac group only 17 of 45 of the elevations (1.8 % of all patients) resolved on therapy.

There were 23 (0.7%) of 3379 patients on any dose of rofecoxib who had AST or ALT elevations >3 times the ULN that did not resolve (i.e., returned to <2 times the ULN) while remaining on study therapy compared with 28 (3.0%) of 497 and 0 (0%) of 847 in the diclofenac and ibuprofen groups, respectively. (narrative for these patients are in Appendix 21.). Fourteen of these 23 rofecoxib patients had other possible explanations for the elevations (in contrast to 5 of 28 of the diclofenac patients). Other possible explanations for the aminotransferase elevations included recent surgery, alcohol consumption, trauma, viral hepatitis, or initiation of new concomitant therapy. Elevations first occurred from 23 to 272 days on study therapy. Six of the 9 patients who had no other explanation for the LFT elevation had isolated elevations in transaminases without associated elevations in bilirubin or alkaline phosphatase. Three patients had an increase in bilirubin and/or alkaline phosphatase coincident with the aminotransferase elevations—AN 5332 (Study 034; 25 mg rofecoxib), AN 5792 (Study 034; 25 mg rofecoxib), and AN 37 (Study 010; 125 mg rofecoxib). Only AN 37 had clinical signs or symptoms associated with the aminotransferase elevations. All transaminase elevations resolved following discontinuation of rofecoxib (Narrative for patients with LFT > 3ULN not resolved while on treatment are in Appendix 22).

7.3.3. Pancreatitis

It is known that COX-2 enzymes are constitutively expressed in the pancreas and it would not be unexpected to find some pancreatic toxicity. However, from this database it is not possible to definitively ascertain the effects of rofecoxib in the pancreas. Four cases of pancreatitis were found in this NDA (approximately 5700 patients in any treatment in controlled OA trials). All were patients on rofecoxib (AN 5126, AN 2231, AN1436 and AN 2105). None of them was considered by the investigator to be related to study drug. (Narratives for the three patients with pancreatitis are in Appendix 23).

Diarrhea (as a possible sign of malabsorption) was very common in all groups and no major work-ups were conducted. Mean serum glucose levels (as a possible sign of an effect on the pancreatic endocrine function) were unaffected; few patients developed hyperglycemia on rofecoxib but the incidence seemed to be similar to that in the active comparator groups. Unfortunately amylase and lipase were not measured routinely.

In summary: The incidence of borderline (>ULN) and notable (>3 ULN) LFT elevations at the doses recommended for the treatment of OA were similar to ibuprofen and lower than diclofenac. There are no adequate PK studies in patients with moderate and severe hepatic insufficiency, therefore, the use of rofecoxib in these patients is not recommended. Four patients developed pancreatitis in the complete database (all four taking rofecoxib); two of them had other possible explanations. A larger database will be needed to answer whether this is a true rofecoxib-related event.

7.4. OVERVIEW OF CARDIOVASCULAR AND RENAL SAFETY

(For a more detailed review the reader is referred to Dr. Pelayo's review (cardio-renal consultant).

NSAIDs are known to reduce renal function when renal perfusion is dependent on prostaglandin formation. Patients at risk for renal failure include those with a variety of renal diseases, congestive heart failure, cirrhosis with ascites, volume depeletion and diuretic use. NSAIDS are also known to produce fluid retention and edema and to interfere with the blood pressure lowering effects of certain antihypertensive medications. These adverse events are now thought to be related at least in part, to COX-2 inhibition, and are thus expected to be seen with rofecoxib.

The results of three clinical pharmacology studies related to renal function (023, 064, 065), all controlled trials in OA and available data in RA, are summarized as follows:

1- There was an association between administration of rofecoxib 12.5 and 25 mg/day and the development of edema similar to the NSAID active comparators and clearly distinguished from placebo.

2- There was an association between administration of rofecoxib 12.5 and 25 mg/day and the development of hypertension and increased BP similar to NSAID active comparators (ibuprofen, diclofenac and nabumetone) and clearly distinguished from placebo.

3- There was a trend suggestive of an increase in the incidence of elevated BUN, serum creatinine, hyperkalemia and proteinuria among patients on rofecoxib and active control groups relative to placebo.

4- All of the above effects were more frequent in ≥ 6-month studies with the dose of 50 mg/day and in 6-week studies with doses of ≥ 125 mg/day. Renal-related toxicity appears to be related to dose and time of exposure. (See tables 44 to tables 49).

In study 029, a 6-week dose ranging study in OA, rofecoxib 50 mg QD did not show dramatic differences from rofecoxib 12.5 and 25 mg in the rate of clinical or laboratory adverse events; for instance, none of 97 patients randomized to the 50 mg group had an adverse event of hypertension. However, in 6-month studies there was a significant increase in the incidence of hypertension and edema, and a trend suggesting a higher incidence of increased creatinine, hyperkalemia, decreased hemoglobin and hematocrit and proteinuria with rofecoxib 50 mg QD.