Table 44. **Study #044/045. Number (%) Of Patients With Hypertensive- or Edema-Type Adverse Experiences or Laboratory Adverse Events Week 18 (Intention-to-Treat Approach)**

Treatment	ΣHypertension n‡/N§ (%)	ΣEdema n‡/N§ (%)	Serum creatinine Increased n‡/N§ (%)	Hyperkalemia n‡/N§ (%)	Proteinuria n‡/N§ (%)
Placebo	13/358 (3.6)	10/361 (2.8)	1/363 (0.4)	9/363 (0.0)	2/363 (0.5)
MK-0966 25 mg	23/367 (6.4)	23/367 (6.3)	5/385 (1.3)	5/385 (0.8)	5/384 (1.3)
MK-0966 50 mg	31/358 (8.6)	30/349 (8.6)	11/372 (2.9)	4/371 (1.1)	3/371 (0.8)
Ibuprofen 2400 mg	17/360 (4.7)	16/361 (4.4)	6/377 (1.6)	3/371 (0.8)	4/371 (1.1)

[Adapted from NDA 21-042. ΣHypertension = Blood pressure increased, Borderline hypertension, Hypertension, Uncontrolled hypertension. ΣEdema = Edema, Fluid retention, Lower extremity edema, peripheral edema, Upper extremity edema. ‡Number of patients with adverse event. §Total number of patients.] (From Dr. Pelayo's review).

Table 45. Study #034C. Number (%) Of Patients With Hypertensive- or Edema-Type or Laboratory Adverse Experiences Entire 1-Year Base Studies All Randomized Patients

Treatment	ΣHypertension n‡/N§ (%)	ΣEdema n‡/N§ (%)	Serum creatinine increased n‡/N§ (%)	Hyperkalemia n‡/N§ (%)	Proteinuria n‡/N§ (%)
MK-0966 12.5 mg	41/490 (8.4)	39/490 (8.0)	7/486 (1.4)	1/486 (0.2)	13/486 (2.7)
MK-0966 25 mg	46/489 (9.4)	45/489 (9.2)	12/483 (2.5)	5/483 (1.0)	19/484 (3.9)
Diclofenac 150 mg	32/498 (6.4)	29/498 (5.8)	13/496 (2.6)	3/496 (0.6)	17/495 (3.4)

[Adapted from NDA 21-042. ΣHypertension = Blood pressure increased+Borderline hypertension+Hypertension. ΣEdema = Edema+Hand swelling+Lower extremity edema+Peripheral edema. ‡Number of patients with adverse event. §Total number of patients.] (From Dr. Pelayo's review).

Table 46. Edema related adverse events. Number (%) of Patients With Specific Edema-Related Clinical Adverse Experiences. 6- Month OA studies. (Table E-109, original NDA).

	Placebo		MK-0966 5 mg		MK-0966 12.5 mg		MK-0966 25 mg		MK-0966 50 mg		MK-0966 125 mg		Ibuprofen 2400 mg	
6-Month Studies (Protocols 044 and 045 and First 6 Months of Protocols 034 and 035)														
	(N=371)[f]		—		(N=490)		(N=879)		(N=379)		—		(N=377)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with one or more edema-related adverse experiences	**10**	**(2.7)**	—	—	**29**	**(5.9)**	**62**	**(7.1)**	**36**	**(9.5)**	—	—	**18**	**(4.8)**
Edema	2	(0.5)	—	—	5	(1.0)	12	(1.4)	5	(1.3)	—	—	4	(1.1)
Fluid retention	2	(0.5)	—	—	1	(0.2)	9	(1.0)	3	(0.8)	—	—	1	(0.3)
Hand swelling	1	(0.3)	—	—	4	(0.8)	5	(0.6)	1	(0.3)	—	—	0	(0.0)
Lower extremity edema	5	(1.3)	—	—	20	(4.1)	37	(4.2)	25	(6.6)	—	—	13	(3.4)
Peripheral edema	0	(0.0)	—	—	1	(0.2)	8	(0.9)	0	(0.0)	—	—	1	(0.3)
Upper extremity edema	1	(0.3)	—	—	1	(0.2)	3	(0.3)	4	(1.1)	—	—	2	(0.5)

In patients with R.A. at the doses of 125 and 175 mg QD (five to eight times the highest recommended dose for OA) for 6 weeks (Study 017), the incidence of edema-related AE was 13.0 % compared to 2.9 % in patients on placebo. During the 16 week extension,

(study 017c) the incidence of edema-related AE was 16.7 % (10/60) compared to 0.0 % (0/13) in patients on ibuprofen.

In study 017, a 6-week study in RA, rofecoxib 125 and 175 mg QD showed a significant increased incidence of hypertension and edema compared to placebo. During the 12-week extension study in RA, seven (11 %) of the 60 patients randomized to rofecoxib 125 mg had hypertension and four were discontinued from the study due to this adverse event.

Table 47. HTN related adverse events. Number (%) of Patients With Specific Edema-Related Clinical Adverse Experiences. 6- Month OA studies. (Table E-111. Original NDA).

	Placebo		MK-0966 5 mg		MK-0966 12.5 mg		MK-0966 25 mg		MK-0966 50 mg		MK-0966 125 mg		Ibuprofen 2400 mg		Diclofenac 150 mg	
6-Month Studies (Protocols 044 and 045 and First 6 Months of Protocols 034 and 035)																
	(N=371)[1]		—		(N=490)		(N=879)		(N=379)		—		(N=377)		(N=498)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with one or more hypertension adverse experiences	13	(3.5)	—	—	28	(5.7)	61	(6.9)	46	(12.1)	—	—	18	(4.8)	15	(3.0)
Blood pressure increased	3	(0.8)	—	—	5	(1.0)	12	(1.4)	6	(1.6)	—	—	2	(0.5)	7	(1.4)
Borderline hypertension	1	(0.3)	—	—	0	(0.0)	0	(0.0)	0	(0.0)	—	—	0	(0.0)	0	(0.0)
Hypertension	8	(2.2)	—	—	22	(4.5)	49	(5.6)	39	(10.3)	—	—	16	(4.2)	8	(1.6)
Hypertensive crisis	1	(0.3)	—	—	0	(0.0)	1	(0.1)	1	(0.3)	—	—	0	(0.0)	0	(0.0)
Systolic hypertension	0	(0.0)	—	—	1	(0.2)	0	(0.0)	0	(0.0)	—	—	0	(0.0)	0	(0.0)
Uncontrolled hypertension	0	(0.0)	—	—	0	(0.0)	0	(0.0)	1	(0.3)	—	—	0	(0.0)	0	(0.0)

Table 48. Patients exceeding predefined limits of change from baseline for creatinine. Six-week, 6-month and 6-month to 86 week studies. From Table E-102, original NDA.

Laboratory test	Predefined limit	Treatment	6-week studies	6-month studies	6- mo to 86 w plus 29-10, 58-
Serum creatinine (mg/dL)	Increase ≥0.5 and value >ULN	Placebo	1/397 (0.3)	1/346 (0.3)	NA
		MK-0966 5 mg	0/142 (0.0)	NA	NA
		MK-0966 12.5 mg	6/713 (0.8)	3/484 (0.6)	5/540 (0.9)
		MK-0966 25 mg	4/720 (0.6)	4/859 (0.5)	11/540 (2.0)
		MK-0966 50 mg	1/93 (1.1)	7/360 (1.9)	5/119 (4.2)
		MK-0966 125 mg	1/73 (1.4)	NA	NA
		Ibuprofen 2400 mg	4/467 (0.9)	6/354 (1.7)	NA
		Diclofenac 150 mg	NA	11/495 (2.2)	4/434 (0.9)
		Nabumetone 1500 mg	1/114 (0.9)	NA	1/85 (1.2)

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Table 49. Patients exceeding predefined limits of change from baseline for serum potassium. All OA studies.

Predefined limit	Treatment	6-week studies	6-month studies	6- mo to 86 w plus 29-10, 58-
Increase ≥0.8 and value >ULN	Placebo	8/395 (2.0)	13/346 (3.8)	NA
	MK-0966 5 mg	1/142 (0.7)	NA	NA
	MK-0966 12.5 mg	23/712 (3.2)	25/484 (5.2)	24/540 (4.4)
	MK-0966 25 mg	23/720 (3.2)	73/859 (8.5)	36/540 (6.7)
	MK-0966 50 mg	3/93 (3.2)	59/359 (16.4)	4/119 (3.4)
	MK-0966 125 mg	0/73 (0.0)	NA	NA
	Ibuprofen 2400 mg	8/465 (1.7)	23/354 (6.5)	NA
	Diclofenac 150 mg	NA	29/495 (5.9)	21/434 (4.8)
	Nabumetone 1500 mg	7/114 (6.1)	NA	4/85 (4.7)

Reviewer's comment: It is not clear to this reviewer what the clinical impact of the above observed events would be once the drug goes into the market. For instance, only patients withdrew due to increased potassium and did not require specific treatment; few patients continued having increased potassium during follow up Similarly, few patients needed to discontinue treatment due to hypertension or increased creatinine (Appendix 22). However, we need to keep in mind that patients in clinical trials are relatively healthy and that patients with a calculated creatinine clearance of < 30 mL/min had been excluded from these studies.

5- Neither patients on rofecoxib nor patients on NSAID comparators presented acute renal failure requiring dialysis, nephrotic syndrome or papillary necrosis, however, two patients on rofecoxib and one patient on ibuprofen were discontinued due to renal insufficiency not requiring dialysis. (Appendix 23).

6- The NDA provides only incomplete data regarding acid-base balance in patients receiving rofecoxib. Analysis of Bicarbonate and Chloride data from study 044 and 045 did not show evidence of adverse effects on acid-base balance but data are limited to approximately 700 patients with 6-month exposure to rofecoxib. Phosphate and Magnesium were not measured.

In summary: The pattern of adverse events reported in this NDA at the doses proposed for use in OA (12.5 and 25 mg QD) is similar to the expected for NSAIDs. It is possible that renal adverse effects may become more problematic when rofecoxib doses of 50 mg or higher are used chronically. There were no unique renal adverse events seen with rofecoxib and different from other NSAIDs. Detecting clinically serious but uncommon renal adverse events will require a larger database.

7.5. THROMBOEMBOLIC AND VASCULAR SAFETY

There is a theoretical concern that patients chronically treated with a COX-2 selective inhibitor may be at higher risk for thromboembolic cardiovascular adverse experiences than patients treated with COX-1/COX-2 inhibitors (conventional NSAIDs), due to the lack of effect of COX-1 inhibition on platelet function. .

Most of the serious adverse events observed in this NDA were of the cardiovascular body system, including MI, unstable angina, CVA and TIA's. Of note, patients with a recent history of MI or unstable angina and with a TIA or CVA within 2 years prior to entry were excluded from the studies, although a significant percentage of the population had a preexisting cardiovascular condition, mostly hypertension (see Table 50 and 51). Additionally, patients taking low dose aspirin or other antiplatelet or anticoagulant medications were excluded from the studies.

Table 50. Baseline demographics and cardiovascular history in elderly and primary 6-week studies.

	Elderly OA Study	Primary 6-Week Studies
Total Number of Patient	**341**	**2457**
Mean Age (years)	83	65
% of Female Patients	64	75
% of Patients with Preexisting Cardiovascular Condition	75	60
% of Patients with Preexisting Hypertension	48	42
% of Patients with Preexisting Angina Pectoris	10	3
% of Patients with Preexisting Myocardial Infarction	11	2
Mean Creatinine Clearance (ml./min)	45	88

[P010; P029; P033; P040; P058]

Table 51. Secondary diagnoses (incidence ≥ 0.5 %) in 6 month OA studies (from Table E-16, original NDA).

	Placebo		Rfx 12.5 mg/d		Rfx 25 mg/d		Rfx 50 mg/d		Ibuprofen		Diclo	
Cardiovascular System	**183**	**(49.3)**	**295**	**(60.2)**	**482**	**(54.8)**	**202**	**(53.3)**	**291**	**(58.4)**	**205**	**(54.4)**
Hypertension	107	(28.8)	206	(42.0)	309	(35.2)	133	(35.1)	194	(39.0)	143	(37.9)
Venous insufficiency	4	(1.1)	19	(3.9)	22	(2.5)	3	(0.8)	27	(5.4)	4	(1.1)

Evaluation of deaths, cardiovascular serious non-fatal and of thromboembolic adverse events in this NDA does not seem to indicate a dose response relationship with rofecoxib (Tables 36. And 37).

Evaluation of CV thromboembolic events regardless of seriousness shows a numerically higher incidence of ischemic/thromboembolic events (angina, myocardial infarction, CVA, TIA) in patients taking rofecoxib when compared with patients taking placebo, but the exposure to placebo was less than the exposure to rofecoxib. In 6 weeks studies there was one event in the placebo group (0.2 %) and a total of 12 events (approximately 1 %) in the rofecoxib groups. In 6 month studies there were 3 events in placebo

(approximately 1%) and 23 (approximately1 %) in the total rofecoxib group, even though placebo patients were only exposed for up to 18 weeks. The data seem to suggest that in 6 –week studies, thromboembolic events are more frequent in patients receiving rofecoxib than placebo but do not show a clear dose response relationship with rofecoxib. There is a trend towards an increased incidence in longer trials, but it is always expected to have some increase in the incidence of adverse events with longer time of observation. The incidence of thromboembolic events with rofecoxib appears to be similar to comparator NSAIDs.

It is difficult to reach meaningful conclusions when the number of events is relatively small and the length of the exposure and doses of rofecoxib used were different among studies. Longer studies included only the 12.5 and 25 mg rofecoxib doses; exposure to the 50 mg dose was limited to 397 patients in 6 month studies and less than 60 patients in 6-month to 86 week studies.

In summary: With the available data, it is impossible to answer with complete certainty whether the risk of cardiovascular and thromboembolic events is increased in patients on rofecoxib. A larger database will be needed to answer this and other safety comparison questions.

Patients who need aspirin for cardiovascular reasons should not stop aspirin when taking rofecoxib. There is a potential concern of increasing the risk of GI bleeding events with the concomitant use of rofecoxib and aspirin but limited data are available from clinical studies with this combination.

Table 52. Thromboembolic adverse events regardless of seriousness. All OA trials.

	6 week studies	6 month studies	6 month to 86 week plus 029-10 and 058-10
	N/n %	N/n %	N/n %
Placebo	**1/412 (0.2%)** Cerebrovascular accident	3/371 (0.8%) Acute myocardial infarction 2 Unstable angina	
Rofecoxib 5	**0/149**		
Rofecoxib 12.5	**5/725 (0.7%)** Myocardial infarction Cerebrovascular accident Coronary artery disease Ischemic heart disease Angina pectoris	**7/490 (1.2%)** Cerebrovascular accident Myocardial infarction 2 Angina pectoris 3 CAD Ischemic heart disease	**7/550 (1.3%)** Angina pectoris 3 CVA CAD Ischemic heart disease Transient ischemic attack
Rofecoxib 25	**5/735 (0.8%)** Myocardial infarction 2 Unstable angina 2 Angina pectoris	**10/879 (1.0 %)** Transient ischemic attack 3 Myocardial infarction 2 Angina pectoris 3 Coronary artery disease 2	**6/547 (1.1%)** Angina pectoris 2 CVA 1 Coronary artery disease Ischemic heart disease Myocardial infarction
Rofecoxib 50	**1/97 (1.1%)** Angina pectoris	**4/379 (1.1%)** Cerebrovascular accident 3 Transient ischemic attack	**3/123 (2.4%)** CVA Coronary artery occlusion Myocardial infarction
Rofecoxib 125	**(1/74) (1.4%)** Transient Ischemic Attack		
Ibuprofen 2400	**(2/470) (0.4%)** Cerebrovascular accident Angina pectoris	**2/377 (0.5%)** Angina pectoris 2	
Nabumetone 1500	0/115		**1/92 (1.1%)** Angina pectoris
Diclofenac 150		**9/498 (1.8%)** Cardiac arrest 2 Myocardial infarction 2 Angina pectoris 2 Coronary artery disease Unstable angina Cerebrovascular accident 2	**6/439 (1.3%)** Myocardial infarction Coronary artery occlusion Coronary artery disease 2 Angina pectoris 2

N/n = number of events/number of patients randomized.

7.6. OVERVIEW of SKIN and APPENDAGES SAFETY

Skin rash and pruritus were seen occasionally in patients with rofecoxib (see table). Serious adverse events related to skin and appendages were skin basal cell carcinoma (also seen in NSAID comparators and placebo) and cellulitis (one case). Few patients discontinued due to adverse event related to the skin. There were no cases of serious allergic skin reactions, anaphylactoid reaction or asthma.

Table 53. Number (%) of Patients With Skin Clinical Adverse Experiences (Incidence ≥ 1.0% in One or More Treatment Groups) by Body System 6- Month Osteoarthritis Studies

	Placebo* (N=371)		MK-0966 12.5 mg (N=490)		MK-0966 25 mg (N=879)		MK-0966 50 mg (N=379)		Ibuprofen 2400 mg (N=377)		Diclofenac 150 mg (N=498)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Skin and Skin Appendages	**22**	**(5.9)**	**56**	**(11.4)**	**185**	**(11.9)**	**60**	**(15.8)**	**23**	**(6.1)**	**51**	**(10.2)**
Basal cell carcinoma	1	(0.3)	2	(0.4)	3	(0.3)	4	(1.1)	0	(0.0)	2	(0.4)
Cellulitis	0	(0.0)	6	(1.2)	4	(0.5)	0	(0.0)	0	(0.0)	2	(0.4)
Herpes zoster	0	(0.0)	3	(0.6)	4	(0.5)	4	(1.1)	0	(0.0)	3	(0.6)
Nail unit disorder	1	(0.3)	3	(0.6)	2	(0.2)	4	(1.1)	1	(0.3)	1	(0.2)
Pruritus	8	(2.2)	13	(2.7)	18	(2.0)	6	(1.6)	3	(0.8)	6	(1.2)
Rash	4	(1.1)	14	(2.9)	21	(2.4)	11	(2.9)	5	(1.3)	11	(2.2)

From Table E-36, original NDA. (The placebo group only has 18-week exposure).

Oral ulcers were a common adverse event (up to 4 % of patients in the RA studies at doses of 125 and 175 mg/day). They were generally mild to moderate in severity and most of them resolved while on treatment.

In summary: There were no particularly concerning skin-related or allergic events with the use of rofecoxib. However, patients with known hypersensitivity to NSAIDs and with the aspirin triad had been excluded from the studies.

7.7. OVERVIEW OF NERVOUS SYSTEM SAFETY

COX-2 enzymes are expressed in the brain. There is a theoretical concern of the possibility of some kind of CNS adverse event with COX-2 inhibitors. In 6 month studies, common adverse events seen with frequency ≥ 2 % in any of the rofecoxib groups were insomnia and depression (Table 54). Insomnia did not appear to be dose related. There is a suggestion of dose-related incidence of depression, but this is a very common condition and 10 % of patients included in OA studies had a previous history of depression or depressive disorder. There was no evidence of unique neurologic events with rofecoxib in this database.

Table 54. Number (%) of Patients With Nervous System Clinical Adverse Experiences (Incidence ≥ 1.0% in One or More Treatment groups), 6- Month Osteoarthritis Studies.

	Placebo' (N=371)		MK-0966 12.5 mg (N=490)		MK-0966 25 mg (N=879)		MK-0966 50 mg (N=379)		Ibuprofen 2400 mg (N=377)		Diclofenac 150 mg (N=498)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nervous System	**44**	**(11.9)**	**68**	**(13.9)**	**131**	**(14.9)**	**56**	**(14.8)**	**50**	**(13.3)**	**80**	**(16.1)**
Headache	33	(8.9)	29	(5.9)	56	(6.4)	30	(7.9)	32	(8.5)	40	(8.0)
Hypesthesia	1	(0.3)	2	(0.4)	8	(0.9)	4	(1.1)	4	(1.1)	5	(1.0)
Insomnia	2	(0.5)	15	(3.1)	18	(2.0)	9	(2.4)	3	(0.8)	8	(1.6)
Migraine	1	(0.3)	1	(0.2)	4	(0.5)	4	(1.1)	0	(0.0)	5	(1.0)
[illegible]uscular spasm	2	(0.5)	0	(0.0)	5	(0.6)	3	(0.8)	2	(0.5)	5	(1.0)
esthesia	1	(0.3)	7	(1.4)	9	(1.0)	4	(1.1)	2	(0.5)	5	(1.0)
moleence	1	(0.3)	2	(0.4)	7	(0.8)	0	(0.0)	3	(0.8)	5	(1.0)
Vertigo	4	(1.1)	7	(1.4)	13	(1.5)	0	(0.0)	1	(0.3)	4	(0.8)
Psychiatric Disorder	**6**	**(1.6)**	**23**	**(4.7)**	**32**	**(3.6)**	**18**	**(4.7)**	**12**	**(3.2)**	**19**	**(3.8)**
Anxiety	2	(0.5)	7	(1.4)	10	(1.1)	6	(1.6)	3	(0.8)	7	(1.4)
Depression	1	(0.3)	6	(1.2)	13	(1.5)	9	(2.4)	3	(0.8)	8	(1.6)

From Table E-36, original NDA. (The placebo group only has 18-week exposure).

The 120-day safety update reports two patients with neurologic adverse events of unclear etiology. Both occurred in study 068, dose ranging study in RA and both were considered by the investigator to be related to rofecoxib, one was on rofecoxib 5 and the other on rofecoxib 25 mg/d. (Narrative of these cases are in appendix 24). However apart from these cases, review of the complete NDA database does not suggest that rofecoxib is associated with concerning nervous system adverse events.

In summary: There were no evidence of concerning nervous system-related adverse experiences in the rofecoxib database.

7.8. OVERVIEW OF RESPIRATORY SYSTEM SAFETY

Respiratory system-related adverse events were common and had similar incidences to placebo. Serious adverse events of pneumonia were evenly distributed among the different treatment groups (see Table 37). There were not unique adverse events related to the respiratory system.

7.9. REPRODUCTIVE SYSTEM

COX-2 is expressed in the reproductive system, therefore, it is conceivable that rofecoxib might have some effects in menstrual cycles and fertility. Pre-clinical data in female rats suggest that there is a partial inhibition of ovulation and decreased fertility at approximately 8 and 3 fold human exposure at 25 and 50 mg daily based on AUC_{0-24}. As with other NSAIDs, there was evidence of early closure of the ductus arteriosus.

There is no evidence of such adverse events in humans in this database. However, no particular questions regarding characteristics of the menstrual cycles (e.g. frequency, regularity) were asked, and pregnant women were not studied. Despite the fact that patients were requested to follow appropriate contraception, six patients became pregnant during the OA studies (Table 55). One patient on rofecoxib gave birth to a normal baby.

Table 55. Pregnancies during rofecoxib clinical studies (original NDA)

Table E-129 Summary of All Pregnancies
All Phase I to III Studies

Protocol	Allocation Number	Treatment	Outcome of Pregnancy
055	AN 4019	Naproxen sodium 550 mg	Carrying to term
056	AN 1011	Naproxen sodium 550 mg	Electively terminated
	AN 1080	Placebo	Electively terminated
	AN 1042	Placebo	Electively terminated
070	AN 043	MK-0966 25 mg	Healthy male infant, born 29JUN98
071	AN 8030	MK-0966 50 mg	Carrying to term

In summary: Rofecoxib is designed Category C for drugs taken during pregnancy. It should not be taken in late pregnancy because, as other NSAIDs, it may cause closure of the ductus arteriosus.

8. Special populations.

8.1. Elderly

After single dose of 25 mg rofecoxib in elderly subjects (over 65 years old) a 34% increase in AUC was observed as compared to the young subjects. The clinical significance of this observation is unknown. In OA clinical studies, approximately 20 % of patients were older than 65; study 058 included 341 patients who were 80 years and older. There were no substantial differences in safety between elderly patients and younger patients, except for higher number of patients with increased creatinine in study 058 (up to 4.2 and 5.6 % of patients for the rofecoxib 12.5 and 50 mg respectively). This incidence was higher than placebo and that the active comparator NSAID (nabumetone) (Table 56). Of note, elderly patients in this study started with a lower mean estimated creatinine clearance than patients in other OA studies (45 mL/min and 88 mL/min respectively).

Table 56. Number (%) of Patients With Specific Laboratory Adverse Experiences by Laboratory Test Category. Elderly Osteoarthritis Study. Base study. (Source Table 60, Safety Update Report)

	Primary 6-Week Data			
		Rofecoxib		Nabumetone
	Placebo (N=52)	12.5 mg (N=118)	25 mg (N=56)	1500 mg (N=115)
	n/m (%)*	n/m (%)*	n/m (%)*	n/m (%)*
Blood Chemistry (Cont.)	**2/52 (3.8)**	**8/118 (6.8)**	**6/54 (11.1)**	**6/114 (5.3)**
Blood pancreatic lipase increased	0/[a]	1/1 (100.0)	0/[a]	0/[a]
Blood urea nitrogen increased	0/52 (0.0)	2/118 (1.7)	1/54 (1.9)	0/114 (0.0)
Creatine phosphokinase increased	0/8 (0.0)	1/21 (4.8)	1/6 (16.7)	0/17 (0.0)
Gamma-glutamyl transpeptidase increased	0/10 (0.0)	1/28 (3.6)	0/10 (0.0)	0/24 (0.0)
Hyperglycemia	2/52 (3.8)	0/118 (0.0)	1/54 (1.9)	1/114 (0.9)
Hyperkalemia	0/52 (0.0)	0/118 (0.0)	2/54 (3.7)	0/114 (0.0)
Hypokalemia	0/52 (0.0)	0/118 (0.0)	1/54 (1.9)	0/114 (0.0)
Hyponatremia	0/52 (0.0)	0/118 (0.0)	0/54 (0.0)	0/114 (0.0)
Serum creatinine increased	0/52 (0.0)	5/118 (4.2)	3/54 (5.6)	4/114 (3.5)
Total serum bilirubin increased	0/52 (0.0)	0/118 (0.0)	1/54 (1.9)	0/114 (0.0)
Uric acid increased	0/52 (0.0)	0/118 (0.0)	0/54 (0.0)	1/114 (0.9)

8.2. Gender and race

The pharmacokinetics, safety, and efficacy of MK-0966 are comparable in men and women. Pharmacokinetic differences due to race have not been studied. In clinical studies, there do not appear to be any differences in efficacy or safety based on race or gender.

8.3. Pediatrics

The pharmacokinetics, safety, and efficacy of MK-0966 were not evaluated in patients younger than 18 years.

9. Drug Interactions

Clinical pharmacology studies with rofecoxib have identified potentially significant interactions with methotrexate, warfarin, ACE inhibitors, rifampin, cimetidine and antacids. The effects of rofecoxib on the pharmacokinetics and/or pharmacodynamics of ketoconazole, prednisone/prednisolone, oral contraceptives, digoxin have been studied *in vivo* and clinically important interactions have not been found.

Methotrexate: Rofecoxib 75 mg and 250 mg administered once daily for 10 days increased plasma concentrations by 23% and 40% respectively, as measured by $AUC_{0-24\ hr}$ in patients with rheumatoid arthritis receiving methotrexate 7.5 to 15 mg/week. An equivalent magnitude of reduction in methotrexate renal clearance was observed. Adequate monitoring of methotrexate-related toxicity should be considered if rofecoxib and is going to be administered to a patient taking methotrexate.

ACE-inhibitors: Administration of 25 mg daily of rofecoxib with an ACE inhibitor (benezapril, 10 to 40 mg) for 4 weeks in patients with mild-to-moderate hypertension, was associated with a small attenuation of the antihypertensive effect (average increase in 24-hour mean arterial pressure of 2.8 mm Hg) compared to ACE inhibitor alone. Of note, in clinical studies, increased incidence of reported hypertension was also seen in patients taking rofecoxib who were not taking ACE inhibitors. Clinical studies and post marketing observations have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. Rofecoxib should be given with caution to patients with hypertension.

Warfarin: A potential of interaction between rofecoxib and warfarin was demonstrated by a small increase in the pharmacodynamic effect of warfarin. An increase in prothrombin time International Normalized Ratio (INR) of approximately 11% and 8% was observed after a single dose of 30 mg warfarin with healthy subjects on 50 mg rofecoxib and after multiple doses of warfarin for 3 weeks with healthy subjects on 25 mg of rofecoxib, respectively. For most indications, the warfarin dose is titrated with the goal of attaining an INR value between 2.0 and 3.0. Monitoring of prothrombin time must be considered when therapy with rofecoxib is initiated in patients on warfarin therapy.

Aspirin: Rofecoxib does not inhibits COX-1 and it is not a substitute for aspirin for cardiovascular prophylaxis. At steady state, rofecoxib 50 mg once daily had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin, as assessed by ex vivo platelet aggregation and serum TXB_2 generated clotting blood in one clinical pharmacology study. Clinical studies in OA provided limited data on the concomitant use of rofecoxib and low dose aspirin (only 61 patients in the whole database). This combination may potentially result in an increased rate of GI ulceration or other bleeding complications.

OVERALL CONCLUSIONS OF ROFECOXIB SAFETY

(Based on Analgesia, OA and submitted RA studies):

1) The general safety profile of rofecoxib at the proposed doses for the treatment of OA (12.5 and 25 mg QD), is clearly distinguishable from placebo and seems to be similar to the NSAID comparators (ibuprofen, diclofenac and nabumetone).

2) Rofecoxib toxicity appears to be related to dose and time of exposure.

3) Hematology safety. Rofecoxib at and significantly above the clinical dose range proposed for use in pain and OA, had no effect on bleeding time and platelet agregation compared to placebo. A dose related incidence of decreased hemoglobin and hematocrit was observed in patients taking rofecoxib. This effect appears to be related to hemodilution.

4) Upper GI safety. Although the large differences in endoscopic gastroduodenal ulcer rates between rofecoxib at 25 and 50 mg QD and ibuprofen 800 mg TID suggested a substantial difference in safety profile, analyses of PUBs (perforation, ulcer and bleeding) and clinical endpoints were not demonstrative of clinically significant differences between rofecoxib, ibuprofen and diclofenac.

5) Cardiovascular and Renal safety. Although no patient developed hypertension at the dose of rofecoxib 50 mg QD in the OA 6-week study, in 6-month OA trials, this dose was associated with higher incidence of hypertension and edema compared to rofecoxib 25 mg QD and ibuprofen 800 mg TID. Rofecoxib 50 mg QD also showed a trend suggestive of an increased risk of developing increased creatinine, hyperkalemia, and proteinuria. The data do not suggest a dose-response relationship for cardiovascular thromboembolic events.

6) The NDA provides incomplete data regarding acid-base balance in patients receiving rofecoxib. However, analysis of bicarbonate and chloride data from approximately 700 patients who received rofecoxib at doses of 25 and 50 mg QD in two 6-month studies did not identify any significant safety issue regarding acid-base balance.

OVERALL CONCLUSIONS OF THE ROFECOXIB PROGRAM

Rofecoxib has demonstrated that it is generally safe and effective for the short term management of acute pain and dysmenorrhea (50 mg QD for up to 5 days) and for the treatment of the signs and symptoms of osteoarthritis (12.5 or 25 mg QD).

The general safety profile of rofecoxib at the proposed doses is clearly distinguishable from placebo and seems to be similar to the NSAID comparators (ibuprofen, diclofenac and nabumetone).

Although the large differences in endoscopically defined gastroduodenal ulcer rates between rofecoxib at the doses of 25 and 50 mg QD and ibuprofen 800 mg TID suggested a substantial difference in safety profile, analyses of meaningful clinical GI endpoints were not demonstrative of clinically significant differences between rofecoxib, ibuprofen and diclofenac. Rofecoxib is not the same as placebo.

APPENDICES TO THE ROFECOXIB SAFETY REVIEW