

Vioxx**Excerpts from primary review of NDA 21-042 - Osteoarthritis**

Submission date (letter):	November 23, 1998.
Review date:	December 1998 – May 1999
Reviewer:	Maria Lourdes Villalba, MD.
Drug name:	VIOXX (Rofecoxib)
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 and 25 mg Oral solution 12.5 mg/5ml and 25 mg/5ml
Reviewer's supervisor:	John Hyde, MD

1.1 EXECUTIVE SUMMARY

Rofecoxib is efficacious in the treatment of the signs and symptoms of osteoarthritis (OA) at the proposed doses (12.5 and 25 mg/day).

The results of the single dose analgesic efficacy of Rofecoxib are robust enough to recommend its approval at the proposed dose (50 mg single dose).

The overall safety profile of Rofecoxib at the proposed doses was similar to comparator NSAIDs. Some data (study 029) suggest that Rofecoxib 50 mg QD may be more effective than 25 mg QD in OA. However, with chronic administration of 50mg QD (studies 044 and 045), the data suggest an increased risk of developing adverse events, particularly renal and gastrointestinal (GI) adverse events.

The applicant is not seeking approval for the indication of treatment of signs and symptoms of rheumatoid arthritis (RA) at this time.

Relevant issues:**1) Dose-response and maximum effect in analgesia and osteoarthritis studies.**

In one pivotal dental pain study (071) Rofecoxib 100 and 200 mg doses were significantly more effective than the 50 mg dose. Also, 50 mg appeared to perform better than 25 mg in a multi-dose acute analgesia study (post-orthopedic surgery).

In a randomized, double blind, placebo controlled six-week dose ranging study (029), the data suggested that Rofecoxib 50 mg QD was more efficacious for OA than the proposed doses. However, in 6-month trials designed to assess GI and general safety (044 and 045) this dose was found to be associated with a numerical increase of general GI, endoscopic and renal related adverse events.

2) Duration of rofecoxib analgesic effect

Although Rofecoxib showed statistical analgesic superiority over placebo for 24 hours following a single dose administration, the available data for later time points were less robust.

3) **Gastrointestinal safety.**

In taking into consideration all GI safety parameters, Rofecoxib does not appear to be the same as placebo. Additionally, chronic dosing at 50 mg QD was associated with numerically more clinical GI adverse events and endoscopic ulcers compared to 25 mg QD.

4) **Effects in acid-base balance.**

Because serum Bicarbonate and Chloride were measured in only two studies, an adverse effect of Rofecoxib on acid-base balance can not be excluded.

1.2. EXCERPTS FROM VIOXX EFFICACY REVIEW

A summary of all OA studies with Vioxx is presented in the next page.

Conclusions from OA efficacy studies with Vioxx

The following conclusions regarding Rofecoxib and treatment of the signs and symptoms of OA are drawn from the information presented in four pivotal clinical trials (033, 040, 034 and 035):

- Rofecoxib, 12.5 and 25 mg once a day, was efficacious vs. placebo in six-week trials.
- Rofecoxib 12.5 and 25 mg once a day was clinically comparable to the efficacy of Ibuprofen 800 mg TID in 6 week trials and to Diclofenac 50 mg TID up to 6 months, when using the criteria of clinical comparability pre-defined by the applicant (± 10 in a 1-100 mm VAS scale or ± 0.5 in a 0-4 point Likert scale).

Additional information is drawn from four randomized controlled trials (029, 044, 045, and 058):

- Rofecoxib 50 mg once a day was statistically significantly more efficacious than 12.5 and 25 mg once a day, in a six week dose ranging study. These data has not been replicated. No other studies were done to look at the efficacy of the 50 mg dose. Limited data from 6-month studies designed to address safety issues, showed that rofecoxib 50 mg QD was associated with numerically higher number of renal-related and GI adverse events.

Table 2 of original review. Study characteristics. All Rofecoxib Osteoarthritis Controlled Trials.

Study #	Duration	Number of Centers	Characteristics	Placebo	(Rofecoxib dose, mg/day)					Comparators			Total
				n	5	12.5	25	50	125	Ibu ³	Diclo ⁴	Nab ⁵	
Phase II													
010	6 weeks	27 US	R, DB, PC (knee only)	72	73			74					219
029		64 US	“ “ “	145	149	144	137	97				672	
Phase III													
033 *	6 weeks	62 US	R, DB, PC & AC	69	219			227		221		736	
040 *		52 non-US	“ “ “ “	74	244			242		249		809	
058		45 US	“ “ “ “ in elderly †	52	118			56		115		341	
034 *	6 months ¹	43	R, DB, AC		231			232		230		693	
035 *		69 US	“ “ “		259			257		268		784	
029-10	6 wk - 6mo	51 US	R, DB, AC		104			148		215		467	
029-20	6 mo-1 year		“ “ “		63			86 75		62		286	
029-30	1 year-18mo		“ “ “		47			62 54		48		211	
034-10	6 mo-86 wk	112 (69 US	R, DB, AC	}	224			218		215		657	
035-10		& 43 non-US)	}										
058-10	6 wk - 6 mo	41 US	R, DB, AC in elderly		81			37		78		196	
044	6 months ²	34 US	R, DB, AC, endoscopic†	177	195			186		184		742	
045		5 US, 31 non-US	“ “ “ “ †	194	195			193		193		775	
All ⁶				783	149	1215	1614	476	74	847	397	115	5771

- Pivotal trials. † “Non-flare” studies. n – number of patients randomized. **1-** Studies 034 and 035 were designed as one year trials; data from these studies was analyzed separately up to 6 months and pooled for analysis for the second six month of the year and the extensions. **2-** These were identical 12 week studies with a 12 week extension. **3-** Ibu: ibuprofen 2400 mg/day. **4-** Diclo: diclofenac 150 mg/day. **5-** Nab: nabumetone 1500 mg/day. R: randomized. DB: double-blind. PC: placebo controlled. AC: Active comparator controlled. **6-** Some patients may have received more than one treatment.

Reviewer's comments regarding dose selection for Vioxx (as written throughout the efficacy review in the original review)

The data reviewed in this NDA confirms that rofecoxib doses of 12.5 and 25 mg QD give the optimal risk/benefit ratio. It also indicates a clear dose-response relationship in terms of efficacy and adverse events. In the six-week dose ranging study (029) the 50 mg/d dose was more efficacious than the 25 mg/d dose with minimal increase in toxicity (mostly fluid retention and edema). However, in six-month studies the 50 mg dose was associated with a numerically higher incidence of hypertension, fluid retention, edema, renal-related laboratory abnormalities and GI adverse events compared to the 12.5 and 25 mg QD doses. (See safety review).

Rofecoxib at the dose of 50 mg QD showed a consistent statistically significant difference in LS Mean changes from baseline when compared to the 25 mg dose for all primary endpoints and most secondary endpoints. The differences between 50 and 25 mg QD were numerically greater than the differences between the 25 and 12.5 mg dose and between the 12.5 and 5 mg dose.

These data have not been replicated. As described below, six-month endoscopic studies (044 and 045) measured only one efficacy endpoint. Safety data from these studies, suggest that there may be some limitations to the chronic use of rofecoxib at doses 50 mg/d. If that were not the case, higher doses should have been explored to prove that rofecoxib, at the most effective dose, was still superior to non-selective NSAIDS regarding GI adverse events.

3. EXCERPTS FROM VIOXX SAFETY REVIEW

2.1.General considerations

The aim of any NDA Safety Review is to find trends or signals that suggest an increased incidence of a given adverse event. For many of the observed safety endpoints, one can assume that the available studies will be “under-powered”. To detect or rule out relatively uncommon adverse events a larger database is always needed. Additionally, patients who participate in clinical trials are judged to be in otherwise general good health, based on medical history, physical examination and routine laboratory tests. Therefore, only post-marketing surveillance will allow appreciating the complete safety profile of a new drug.

This review will attempt to give an overview of general safety in the Rofecoxib program. RENAL, GI and HEMATOLOGY safety issues will be discussed in greater detail in reviews provided by the consultants from the relevant FDA review divisions.

2.2.Exposure

This NDA includes information on 5435 patients exposed to rofecoxib. Total exposure to rofecoxib (all trials including Phase I, II and III, OA and RA) up to the cutoff date of March 31, 1998 is shown in Table 29.

Table 29. Total exposure to Rofecoxib in all Trials*

	Any	≥ 1 Week	≥ 2 Weeks	≥ 2 Months	≥ 6 Months	≥ 1 Year
Any dose	5435	4007	3763	1971	1396	822
<12.5 mg	334	161	137	2	0	0
12.5 to <25 mg	1489	1275	1228	582	446	371
25 to <50 mg	2406	1863	1763	902	663	381
50 to <100 mg	1435	675	556	428	272	63
>100 mg	470	286	190	41	2	0

* Data source: calculated from Table E-5 of the original NDA. Of note, some patients may have taken two or more different doses.

As seen in Table 29 and Table 30, the bulk of the exposure to rofecoxib has been to the 12.5, 25 and 50 mg doses. Most of the exposure for ≥ 6 months has been to 12.5 and 25 mg QD. A total of 371 and 381 patients have received 12.5 and 25 mg daily for more than one year. Two hundred and seventy two patients have received 50 mg QD for ≥ 6 months (265 in OA trials); the rest of the exposure to ≥ 50 mg has been in short-term studies. Phase I studies were mostly single dose (ranging from 7.5 to 1000 mg) or short-term multiple-dose studies (up to 375 mg for up to 2 weeks). Analgesia studies were also mostly single dose (ranging from 7.5 to 500 mg) or short-term multiple dose up to 50 mg QD for 5 days. The exposure to rofecoxib exceeds the ICH minimal requirements for establishing safety of a new compound (300 patients for 6 months and 100 patients for one year).

Table 30. Exposure to Rofecoxib in Analgesia studies.

Number of Patients on MK-0966 in the Analgesia Population by Dose and Exposure

Dose of MK-0966	Number of Patients Treated
Any Dose	1002
Single-Dose Exposure	
7.5 mg	87
12.5 mg	72
25 mg	257
50 mg	447
100 mg	91
200 mg	50
250 mg	8
500 mg	20
>1 to ≤5 Doses	
25 mg	17
50/25 mg [†]	84
50 mg	48
[†] 50 mg as an initial dose followed by 25 mg daily 1 or more times. Although some patients may have taken two or more different dosages, they have been counted only one time each, on the "Any dose" row.	

[P038; P055; P056; P072; P004; P027; P051; P066; P071]

Table 31. Total exposure to Rofecoxib in OA Trials

	Any	≥ 1 Week	≥ 2 Weeks	≥ 2 Months	≥ 6 Months	≥ 1 Year
Any dose	3595	3529	3439	1927	1385	818
<12.5 mg	161	146	137	2	0	0
12.5 mg	1282	1260	1228	582	446	371
17.5 mg	1	0	0	0	0	0
25 mg	1732	1696	1662	902	663	381
50 mg	540	515	505	420	265	63
>50 mg	77	70	62	0	0	0

Data Source: calculated from Table E-7 of the original NDA. Patients may have received more than one treatment.

Table 32. Total number of patients randomized to each treatment group in OA trials.

Placebo	Rofecoxib (mg/day)					Comparators (mg/day)			Total
	5	12.5	25	50	125	Ibuprofen 2400	Diclofenac 150	Nabumetone 1500	
783	149	1215	1614	476	74	847	498	115	5771

Patients may have received more than one treatment. Patients who went into extensions and continued on the same treatment were counted only once. Patients who received a different treatment in the extension, were counted twice.

2.3. Procedures involved in safety monitoring of this NDA (omitted).

2.4. Some limitations of the Rofecoxib database

- 1) Most of the data for comparisons to placebo come from 6-week placebo controlled studies (010, 029, 033, 040 and 058). Only two studies (044 and 045) collected data on placebo patients up to 18 weeks (380 patients). Study 034 and 035 were not placebo-controlled.
- 2) It was somewhat difficult to ascertain the exact exposure to different treatments in this NDA. Safety data were presented divided into four groups: six-week, six-month, one-year and six-month to 86-week studies.

Table 35. Contribution of different studies to study groupings in OA trials

	010	029	033	040	058	034/035	044/045
<u>Study group</u>							
6-week	x	x	x	x	x		
6-month						First 6 mo	x
One-year						Complete year	
6-month to 86-week		029-20 and 029-30 extensions				Second 6 mo and extensions	

(Source, original NDA)

Study 029-10, a crossover study and first extension to study 029, covered the period from 6 weeks to 6 months of the study. These patients were not included in the above study groupings because they were considered to “represent a selected subset of the randomized population”, however, patients from study 029-20 and 029-30 (second and third extensions to study 029) were included among the 6 month-to 86-week studies. Data from studies 034 and 035 were divided into 6-month and 6-month to 86-week

studies, therefore most of the patients who appear in the 6-month to 86-week group are actually the same patients who were in the first 6 months of the studies. Additionally, some adverse event tables pooled studies 029-10 and 058-10 with the 6-month to 86-week studies.

- 3) For survival analyses, patients who had received placebo in the base studies and active treatment in the extensions, were counted by the applicant as if they had received only the active treatment (reducing the denominator for placebo patients).
- 4) There is no open label experience in patients with OA. The “dose-creep” phenomenon has been described in the past with other NSAIDs and recently with celecoxib. Safety data for the chronic use of rofecoxib 50 mg QD are limited to 397 patients for 6 months and 40 patients for up to 86 weeks. Although the doses proposed to be used for the acute and chronic symptoms of OA are 12.5 and 25 mg QD, the dose proposed to be used for management of acute pain and dysmenorrhea is 50 mg single dose for up to 5 days.
- 5) There are limited data of the safety of rofecoxib in RA patients.

2.5. DEATHS

There were a total of sixteen deaths in the complete rofecoxib program. Ten deaths were listed in CRF in the original NDA submission (two of them were on rofecoxib 12.5 mg/d, seven were on diclofenac 150 mg/d and one was on naproxen 550 mg). Six deaths were under study blind at the time of NDA submission but additional information was provided with the 120 day Safety Update. (Two of them were on rofecoxib 12.5 mg/d, one was on rofecoxib 50 mg/day, one on placebo, one on diclofenac and one on nabumetone.

Table 36. Deaths (including original NDA submission and 120-day safety update data)

Deaths listed in Case Report Forms in original NDA 21-042:			
Protocol allocation	AN Number	Cause of Death	Treatment
1) 029-10	2395	CORONARY VESSEL OCCLUSION	Diclofenac 150 mg/d
		MULTISYSTEM FAILURE	
2) 034	5599	MYOCARDIAL INFARCTION	“
3) 034	5068	SUICIDE	“
4) 034	5320	CVA,HEMORRHAGIC	“
5) 034-10	5761	POST OPERATIVE COMPLICATION	“
6) 035	7517	CARDIORESPIRATORY ARREST	“
7) 035	7588	DEATH FROM UNSPECIF NATURAL CAUSES	Rofecoxib 12.5 mg/d
8) 035	7922	ADVANCED SYSTEMIC ATHEROSCHLEROSIS	Diclofenac 150 mg/d
9) 040	9415	PULMONARY EMBOLISM	Rofecoxib 12.5 mg/d
10) 072	9089	MULTI SYSTEM FAILURE, SEPSIS	Naproxen
Deaths under study blind at the time of the original submission:			
11) 045	0282	ADENOCARCINOMA OF THE COLON	Placebo
12) 035	7932	MYOCARDIAL INFARCTION	Diclofenac 150 mg/d
13) 058	1283	CARDIAC ARREST	Rofecoxib 12.5 mg/d
14) 058	1502	MULTIPLE ORGAN FAILURE, SEPSIS	Rofecoxib 12.5 mg/d
15) 058	1614	MYOCARDIAL INFARCTION	Nabumetone 1500 mg/d
16) 068	2190	RESPIRATORY FAILURE	
		PULMONARY FIBROSIS	Rofecoxib 50 mg/d

Following is a narrative summary of the deaths on rofecoxib (Narratives for the other deaths are in Appendix 13)

AN 7588, Study 035. 79 year-old white female, history of hypertension and hypothyroidism, MI in 1985 and known LBBB, on methyl dopa/hctz, estrogen, levothyroxine, vitamin C and vitamin K, randomized to Rofecoxib 12.5mg a day on 2/4/97. The patient was seen by friends in her usual state of health on (52 days of study treatment). A few hours later she was found dead. The cause of death was listed in the CRF as unspecified natural causes. (In Appendix 14.4.1 of the NDA, (narrative) the cause of death was reported to be **sudden cardiac death**). No autopsy was performed. Review of CRF shows that on 4/30/97 she had a decreased potassium (3.1) attributed to concomitant medications. No other information is available. The episode was felt by the investigator to be definitively not related to study drug.

AN 9415, Study 040. 80-year-old female with history of hypertension and varices, randomized to **rofecoxib 12.5 mg/d**, died of a **pulmonary embolism** 8 days after sustaining a hip fracture. The patient had entered the study on 9/16/97 and had discontinued from the study 2 weeks prior to the hip fracture due to a clinical adverse event (nonserious facial rash, possibly related to study drug, on 10/24/97). Neither the hip fracture nor the pulmonary embolism were determined by the investigator to be drug related.

AN 1283 (12.5 mg rofecoxib, study 058). 86-year-old woman with a **history of chronic atrial fibrillation** and Paget's disease, who died of cardiac arrest on day 179 of the study. The patient was on no anticoagulation or rate-controlling therapy before or during the study. Electrocardiogram (ECG) at baseline and Day 46 demonstrated atrial fibrillation with a ventricular response of 83 and 65, respectively. On several occasions at study visits, the patient's pulse was noted to be irregular. The patient's last known dose of study medication was on Day 173. On Day 179, the patient was found dead at her home where she lived alone. No autopsy was performed. The **cardiac arrest** was determined by the investigator not to be related to study therapy.

AN 1502 (12.5 mg rofecoxib, study 058). A 87-year-old woman with a history of **angina, hypertension, and cholelithiasis**, died of bacterial sepsis and multiple organ failure due to acute gangrenous gallbladder. The patient was on study medication for 164 days at the time of the onset of **atrial fibrillation**, causing the patient to present to the emergency room. A diagnosis of **ascending cholangitis** was made and on the following day, bacterial sepsis was diagnosed and study drug was discontinued. No surgical intervention was performed. Nine days after the last dose of study therapy, there was onset of **multiple organ failure**, involving respiratory, renal, and hepatic systems. The patient died the next day. Neither the bacterial sepsis nor the multiple organ failure were determined by the investigator to be drug related.

AN 2190 (rofecoxib 50 mg, study 068). A 70 year-old woman with severe R.A., and a history of interstitial lung disease, entered the protocol on 3/30/98. Concomitant medications included methotrexate 10 mg/week. On 4/16/98 (17 days into the study) presented to the investigator with flu-like symptoms and SOB and was found to have scattered ronchi on the right lung. She was prescribed atrovent nasal spray and ceftin for treatment of upper respiratory infection. On patient presented to the E.R. with increasing SOB, fever and was found to have a WBC of 20,000. She received multiple medications (including furosemide, digoxin, antibiotics, solumedrol) for treatment of presumptive CHF, CAD, atrial fibrillation, and pneumonitis. Patient died on 5/10/98. A limited autopsy was performed. The cause of death was respiratory failure with pulmonary fibrosis as a contributing factor. Additional finding was mediastinal emphysema.

Reviewer's comment: Evaluation of the reviewed causes of death among rofecoxib patients did not point out to a particularly concerning trend.

2.6. Clinical and laboratory adverse events other than deaths.

Safety in Analgesia studies is reviewed in detail by Dr. Averbuch. The only significant safety issue encountered in the analgesia studies was postextraction alveolitis ("dry socket"), seen only in the Post-Dental Surgery Studies. The incidence of postextraction alveolitis differed significantly from placebo at the dose recommended for initial treatment of pain, 50 mg but was similar to naproxen sodium and somewhat higher than ibuprofen. Adverse events in Phase I and Clinical Pharmacology studies were no different from the ones seen in OA controlled trials. Because the doses used in the RA study were higher than the doses used in OA studies, this safety review will be divided into two sections: safety in OA and safety in RA, followed by a safety review by body system.

2.6.1. SAFETY IN OA STUDIES

Adverse event data from OA trials were presented in three groups :

- 6 week OA studies (010, 029, 033, 040, 058)
- 6 month OA studies (034 & 035 (first 6 months), 044, 045)
- 6 month to 86 weeks OA studies (034 and 035 -second 6 months-, 29-20/30, 34-10, 058-10)

2.6.1.1. Clinical Adverse Experiences (EXERPT)

a) Serious Non-fatal Clinical Adverse Experiences (See Table 37)

Table 37 lists serious nonfatal adverse events in 6-week studies, 6-month, and 6-month to 86 week studies for each treatment group (musculoskeletal, skin- related and malignancies are not listed).

Serious AE were defined as fatal, life threatening, permanently disabling, requiring or prolonging inpatient hospitalization, as a congenital anomaly, as cancer or as an overdose.

Reviewer's comment: The most frequent serious adverse events were of the cardiovascular body system in all study groupings. 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.

FOR A DETAILED REVIEW THE READER IS REFERRED TO THE ORIGINAL REVIEW.

b) Most common clinical adverse events (omitted).

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

6-week studies	6-month studies	
Placebo (412) Atrial fibrillation Cerebrovascular accident Rofecoxib 5 mg/day (149) Pancreatitis Rofecoxib 12.5 mg/day (725) Vasovagal reaction Myocardial infarction Congestive heart failure Chest pain Cerebrovascular accident Coronary artery disease Pneumonia Rofecoxib 25 mg/day (735) 2 Pneumonia 2 Atrial fibrillation/arrhythmia 2 Myocardial infarction 2 Unstable angina Rofecoxib 50 mg/day (97) none Rofecoxib 125 mg/day (74) Gastrointestinal bleeding Ibuprofen 2400 mg/day (470) Cerebrovascular accident Chest pain Depression Tracheobronchitis Hyperglycemia Nabumetone 1500 mg/day (115) Pneumonia Congestive heart failure Hematochezia	Placebo (371) Acute myocardial infarction 2 Unstable angina Rofecoxib 12.5 mg/day (490) Cerebrovascular accident Myocardial infarction 2 Chest pain 2 Pain Atrial fibrillation/syncope Anxiety disorder Headache Duodenal ulcer Intestinal obstruction 2 Pneumonia Rofecoxib 25 mg/day (594) Syncope Syncope on urination Transient ischemic attack 2 Atrial fibrillation 2 Myocardial infarction 2 Angina pectoris Coronary artery disease 2 Gastrointestinal bleeding Gastric ulcer/ GI obstruct Bronchitis Pneumonia Rofecoxib 50 mg/day (382) Chest pain 2 Cerebrovascular accident 3 Transient ischemic attack Migraine Hypertension Nausea/ vomiting Chest pain / dyspnea / SLE Hyperthyroidism Deep venous thrombosis Gastrointestinal perforation Vomiting / diverticulitis Bacterial infection	Ibuprofen 2400 mg/day (377) Angina pectoris Chest pain Brain abscess Dizziness Vomiting 2 Sick sinus syndrome Diclofenac 150 mg/day (498) Cardiac arrest Myocardial infarction Chest pain Angina pectoris Coronary artery disease Cerebrovascular accident Aortic valve stenosis Cholelithiasis 2 Intestinal diverticulitis Pseudomemb colitis Osteonecrosis Pneumonia 3 Pneumothorax Cellulitis

(n)= number of patients randomized to the studies.

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) Chest pain Hypertension/ BP increased 2 Congestive heart failure Atrial fibrillation 2 Atrial fib/neurological disorder Cerebrovascular accident Peripheral vascular disorder Arterial occlusion Deep venous thrombosis 2 Aortic atherosclerosis Pancreatitis Cholelithiasis Pneumonia Bacterial sepsis Urinary tract infection Polymyositis Rofecoxib 25 mg/day (435) Chest pain 2 Coronary vasospasm Angina pectoris 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)	Rofecoxib 50 mg/day (123) CHF/myocardial infarction Coronary artery occlusion Weight gain/Chest pain/ CHF Gastrointestinal bleeding Pneumonia Cellulitis	Diclofenac 150 mg/day (409) Myocardial infarction Coronary artery disease Angina pectoris 2 Chest pain Vascular insufficienc Tachycardia Anemia Metabolic encephalopathy Bronchitis Pneumonia Intestinal diverticulitis Esophageal ulcer Intestinal obstruction Urinary tract infectio Urolithiasis Appendicitis Cellulitis Nabumetone 1500 mg/day (92) Atrial fibrillation/CHF Chest pain/ CHF
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(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

A summary of laboratory adverse experiences is presented in the tables below. For more detailed information the reader is referred to the original review.

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 $\geq 0.5\%$ of patients. Includes Phase II and III 6-week studies. * BUN was not measured in study 010. Nabumetone was not included in the table.

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

	Placebo* N=363 n (%)	Rofecoxib			Ibuprofen 800 mg TID (N=371) n (%)	Diclofenac 50 mg TID (N=496) n (%)
		12.5 mg/d QD N=486 n (%)	25 mg/d QD N=868 n (%)	50 mg/d QD N=372 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 $\geq 0.5\%$ Source Table E-87 of NDA., Study 044, 045, first 6 months of 034 and 035)

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 NDA 21-042 / 21-052

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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	14 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.

Data Source: [4.20]

2.7. Safety by body system

7.1. OVERVIEW OF HEMATOLOGY SAFETY

For a more detailed review the reader is referred to the original reviews by Drs. Villalba (primary) and Farrell (Hematology Consultant).

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.

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

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
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		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.).

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 depletion 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.

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. Σ Hypertension = Blood pressure increased, Borderline hypertension, Hypertension, Uncontrolled hypertension. Σ Edema = 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	Σ Hypertension n‡/N§ (%)	Σ Edema 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. Σ Hypertension = Blood pressure increased+Borderline hypertension+Hypertension. Σ Edema = 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					Ibuprofen 2400 mg
		5 mg	12.5 mg	25 mg	50 mg	125 mg	
6-Month Studies (Protocols 044 and 045 and First 6 Months of Protocols 034 and 035)							
	(N=371) [‡]	—	(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					Ibuprofen 2400 mg	Diclofenac 150 mg
		5 mg	12.5 mg	25 mg	50 mg	125 mg		
6-Month Studies (Protocols 044 and 045 and First 6 Months of Protocols 034 and 035)								
	(N=371) [‡]	—	(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, 58-10
Serum creatinine (mg/dL)	Increase ≥ 0.5 and value $> \text{ULN}$	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)

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, 58-10
Increase ≥ 0.8 and value $> \text{ULN}$	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 $< 30 \text{ mL/min}$ 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 (approximately 1 %) 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%)	3/371	(0.8%)		
	Cerebrovascular accident		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. 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.

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 $\geq 2\%$ 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 $\geq 1.0\%$ in One or More Treatment groups), 6- Month Osteoarthritis Studies. From Table E-36, original NDA. (The placebo group only has 18-week exposure).

	Placebo [†] (N=371)	MK-0966			Ibuprofen 2400 mg (N=377)	Diclofenac 150 mg (N=498)
		12.5 mg (N=490)	25 mg (N=879)	50 mg (N=379)		
	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)
Muscular spasm	2 (0.5)	0 (0.0)	5 (0.6)	3 (0.8)	2 (0.5)	5 (1.0)
Paresthesia	1 (0.3)	7 (1.4)	9 (1.0)	4 (1.1)	2 (0.5)	5 (1.0)
Somnolence	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)

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.

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			
	Placebo (N=52)	Rofecoxib		Nabumetone
		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	0/52 (0.0)	1/1 (100.0)	0/54 (0.0)	0/114 (0.0)
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 (benazepril, 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

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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 inhibit 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 TXB₂ 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 aggregation 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.