Appendix 12. Study 058. Results. Primary analyses AT 6 weeks.

Analysis of End Point: Patient Global Assessment of Disease Status (VAS)
Mean Change From Baseline (Randomization Visit)
Week 6
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LSMean[1] Change	95% CI for LSMean[1] Change
Placebo	52	63.40	54.23	-9.17	23.18	-14.85	(-23.34, -6.37)
12.5 mg	118	66.58	44.58	-22.00	27.05	-25.34	(-31.60, -19.07)
25 mg	54	64.67	44.33	-20.33	29.50	-25.40	(-33.78, -17.02)
Nabumetone	114	65.58	44.13	-21.45	27.59	-25.95	(-32.58, -19.33)

Comparisons Between Treatment Groups	Difference in LSMean	95% CI for Difference	p-Value
With Placebo			
12.5 and 25 mg vs. Placebo	-10.51	(-18.44, -2.58)	0.010
12.5 mg vs. Placebo	-10.48	(-18.72, -2.25)	0.013
25 mg vs. Placebo	-10.55	(-20.08, -1.01)	0.030
Nabumetone vs. Placebo	-11.10	(-19.35, -2.85)	0.009
Between MK-0966 Doses			
25 mg vs. 12.5 mg	-0.06	(-8.18, 8.06)	0.988
With Active Comparator			
12.5 mg vs. Nabumetone	0.62	(-5.87, 7.10)	0.852
25 mg vs. Nabumetone	0.55	(-7.59, 8.70)	0.893

Effect:	p-Value	Pooled SD
Study Center	0.109	24.93
Baseline Covariate	<0.001	
Treatment	0.045	

[1] Least square mean.

Data Source: [4.47]

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A.12.2. Analysis of primary endpoint AVERAGED over 6 weeks.

Analysis of End Point: Patient Global Assessment of Disease Status (VAS)
Mean Change from Baseline (Randomization Visit)
Averaged over 6-Week Treatment Period
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean[a] Change	95% CI for LS Mean[a] Change
Placebo	52	63.40	56.58	-6.82	18.94	-12.72	(-19.21, -6.23)
12.5 mg	118	66.58	43.99	-22.59	22.97	-25.73	(-30.52, -20.93)
25 mg	54	64.67	44.74	-19.93	24.35	-25.01	(-31.42, -18.61)
Nabumetone	114	65.58	45.09	-20.49	21.50	-24.96	(-30.03, -19.90)

Comparisons Between Treatment Groups	Diff. in LSmean	95% CI for Diff.	p-Value
<u>With Placebo</u>			
12.5 and 25 mg vs. Placebo	-12.65	(-18.71, -6.58)	<0.001
12.5 mg vs. Placebo	-13.00	(-19.30, -6.71)	<0.001
25 mg vs. Placebo	-12.29	(-19.58, -5.00)	0.001
Nabumetone vs. Placebo	-12.24	(-18.55, -5.93)	<0.001
<u>Between MK-0966 Doses</u>			
25 mg vs. 12.5 mg	0.71	(-5.50, 6.92)	0.822
<u>With Active Comparator</u>			
12.5 mg vs. Nabumetone	-0.76	(-5.72, 4.20)	0.763
25 mg vs. Nabumetone	-0.05	(-6.28, 6.18)	0.987

Effect:	p-Value	Pooled SD
Study Center	0.103	19.07
Baseline Covariate	<0.001	
Treatment	<0.001	

[a] Least squares mean

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A.12.3. Study 058

Analysis of End Point: Pain Walking on a Flat Surface (WOMAC)
Mean Change from Baseline (Randomization Visit)
Averaged over 6-Week Treatment Period
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean* Change	95% CI for LS Mean* Change
Placebo	52	56.98	51.70	-5.28	25.53	-4.31	(-11.02, 2.41)
12.5 mg	117	53.11	41.45	-11.66	23.42	-13.08	(-18.09, -8.07)
25 mg	54	54.76	40.27	-14.49	26.86	-14.95	(-21.58, -8.32)
Nabumetone	115	56.27	41.75	-14.52	25.18	-14.26	(-19.51, -9.01)

Comparisons Between Treatment Groups	Diff. in LSmean	95% CI for Diff.	p-Value
With Placebo			
12.5 and 25 mg vs. Placebo	-9.71	(-15.94, -3.48)	0.002
12.5 mg vs. Placebo	-8.78	(-15.25, -2.30)	0.008
25 mg vs. Placebo	-10.64	(-18.14, -3.15)	0.006
Nabumetone vs. Placebo	-9.95	(-16.43, -3.48)	0.003
Between MK-0966 Doses			
25 mg vs. 12.5 mg	-1.87	(-8.25, 4.52)	0.565
With Active Comparator			
12.5 mg vs. Nabumetone	1.18	(-3.95, 6.28)	0.651
25 mg vs. Nabumetone	-0.69	(-7.09, 5.71)	0.832

Effect:	p-Value	Pooled SD
Study Center	0.904	19.60
Baseline Covariate	<0.001	
Treatment	0.013	

*Least squares mean

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Appendix 12.4. Study 058.

Analysis of End Point: SF36: Physical Function
Mean Change from Baseline (Randomization Visit)
Week 6
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LS Mean* Change	95% CI for LS Mean* Change
Placebo	50	32.90	34.07	1.17	14.00	1.50	(-4.34, 7.34)
12.5 mg	114	27.51	33.39	5.88	18.71	4.76	(0.43, 9.09)
25 mg	53	32.31	36.62	4.30	16.84	4.19	(-1.23, 10.22)
Nabumetone	106	30.43	34.07	3.65	18.02	3.35	(-1.24, 7.93)

Comparisons Between Treatment Groups	Diff. in LSmean	95% CI for Diff.	p-Value
With Placebo			
12.5 and 25 mg vs. Placebo	3.13	(-2.35, 8.61)	0.262
12.5 mg vs. Placebo	3.27	(-2.44, 8.97)	0.261
25 mg vs. Placebo	3.00	(-3.57, 9.56)	0.370
Nabumetone vs. Placebo	1.85	(-3.89, 7.59)	0.527
Between MK-0966 Doses			
25 mg vs. 12.5 mg	-0.27	(-5.85, 5.32)	0.925
With Active Comparator			
12.5 mg vs. Nabumetone	1.42	(-3.11, 5.94)	0.538
25 mg vs. Nabumetone	1.15	(-4.48, 6.78)	0.688

Effect:	p-Value	Pooled SD
Study Center	0.962	16.90
Baseline Covariate	<0.001	
Treatment	0.697	

* Least squares mean

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2. ROFECOXIB 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).

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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[1]	84
50 mg	48

[1] 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.

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2.3.Procedures involved in safety monitoring of this NDA .

At each visit, patients were asked whether they had any adverse experience (AE). All AE were entered electronically into a Case Report Form (CRF) of each visit and rated as to intensity, action taken and drug relationship. At each visit, blood and urine samples were obtained (Table 33) and analyzed by a central laboratory (Medical Research Laboratories, Highland Heights, KY). Expected limits of change for vital signs and laboratory measurements are in Table 34. Adverse experiences reported by the investigator were coded into a dictionary of preferred terms called MEDCLASS (Merck's own dictionary).

Table 33. Laboratory Safety tests (study 035)

Laboratory Safety Tests

Hematology	Blood Chemistry
Hemoglobin	Blood Urea Nitrogen (BUN)
Hematocrit	Creatinine
WBC (total and differential)	Total bilirubin*
Platelets	SGOT (AST)
Urinalysis‡	SGPT (ALT)
pH	Alkaline phosphatase
Protein‡	Glucose
Glucose	Sodium
Microscopic: WBCs RBCs	Potassium
Other	Uric acid
Stool HEMOCCULT™ (Screening only)	Calcium
Serum β-HCG (Screening only)	Total protein
Urine β-HCG	Albumin
	Creatinine phosphokinase‖

* Was fractionated (direct/indirect) if elevated.
† CHEMSTRIP 9™, (Boehringer-Mannheim Corporation, Indianapolis, IN) (or equivalent). Microscopy and other appropriate studies (as needed) if CHEMSTRIP 9™ (or equivalent) indicated the presence of any significant abnormality.
‡ Ratio of urine protein to urine creatinine obtained at baseline and any visit where dipstick protein was positive.
‖ Was performed if AST/ALT were elevated.

Data Source: [3.2]

Reviewer's comment: Only study 044 and 045 measured Chloride and Bicarbonate.

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Table 34. Predefined Limits of Change from Baseline for Laboratory and Vital Signs.

Definition of Predefined Limits of Change From Baseline

Parameter (Unit)	Definition*
Hematology	
Hematocrit (%)	Absolute decrease ≥6
Hemoglobin (g/dL)	Increase ≥20% and >ULN Absolute decrease ≥2
Total WBC ($x10^3/\mu L$)	Increase ≥20% and >ULN Decrease ≥20% and <LLN
Lymphocyte count ($x10^3/\mu L$)	Increase ≥20% and >ULN Decrease ≥20% and <LLN
Neutrophil count ($x10^3/\mu L$)	Increase ≥50% and >ULN Decrease ≥20% and <LLN
Platelet count ($x10^3/\mu L$)	Increase ≥50% and >ULN Decrease ≥25% and <LLN
	Increase ≥50% and >ULN
Blood Chemistry	
Bilirubin (mg/dL)	Increase ≥50% and >ULN
Alkaline phosphatase (μ/L)	Increase ≥50% and >ULN
AST (μ/L)	Increase ≥100% and >ULN
ALT (μ/L)	Increase ≥100% and >ULN
Creatinine (mg/dL)	Absolute increase ≥0.5 and >ULN
Uric acid (mg/dL)	Increase ≥50% and >ULN Decrease ≥50% and <LLN
Potassium (mEq/L)	Absolute decrease ≥0.8 and <LLN Absolute increase ≥0.8 and >ULN
Sodium (mEq/L)	Absolute decrease ≥8 and <LLN Absolute increase ≥8 and >ULN
Calcium (mg/dL)	Absolute increase ≥1.5 and >ULN Absolute decrease ≥1.5 and <LLN
Urinalysis	
Protein	Increase ≥1
Vital Signs	
Diastolic BP (mm Hg)	Increase >15 and value >90
Systolic BP (mm Hg)	Increase >20 and value >140
Body weight (kg)	Increase >5 kg

ULN = Upper limit of normal; LLN = Lower limit of normal.
* Changes compared with baseline, defined as the last laboratory value prior to the Flare/Randomization Visit before the first randomized dose.

Source, Table 6, study 034, original NDA.

Reviewer's comment: Patients who started with a high normal or low normal laboratory value needed to have a substantial change from baseline in order to be considered abnormal (for instance a patient with an potassium of 3.5 needed to be down to 2.7 mEq/L).

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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
Study group							
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.

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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 MULTISYSTEM FAILURE	Diclofenac 150 mg/d
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 methyldopa/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 5/23/97 (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.

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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 4/20/98 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.

There were many factors involved in the death of patient AN 2190 (rofecoxib 50 mg). This patient had a history RA with interstitial lung disease and was taking methotrexate. On the day of admission to the hospital the patient had a fever and an elevated WBC suggesting an infection but according to the CRF, she was also treated for presumptive CHF and CAD. The patient had no previous history of cardiovascular disease and her lung disease was stable; she was on no medications for her lung disease and had a normal physical examination at the time of study entry (18 days prior to death). The cause of death for this patient is not completely clear to this reviewer.

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

a) Serious Non-fatal Clinical Adverse Experiences (See Table 37, page 83)

Table 34 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.

- Serious non-fatal adverse events in 6-Week Osteoarthritis Studies (Table 37)

In 6-week studies, the overall incidence and distribution by body system of serious adverse experiences were similar between rofecoxib groups and placebo. Of note the only serious adverse event due to GI bleeding was in a patient on rofecoxib 125 mg QD (AN 1140). There were 14 patients with nonfatal serious cardiovascular adverse experiences. All had cardiovascular risk factors. Only one case (AN 1291, CHF in nabumetone group) was felt by the investigator to be drug related. The incidence of thromboembolic cardiovascular adverse events was similar between the rofecoxib groups and NSAID comparators.

Six patients had serious musculoskeletal adverse experiences; seven patients had skin related events. Two malignancies and one pancreatitis were reported in the rofecoxib 5 mg group (study 029); one head trauma, one malignancy and one GI bleeding were reported in the rofecoxib 125 mg group. (This patient, AN 1140, developed stool positive for occult blood after 2 weeks into study therapy. Endoscopy revealed gastric and

duodenal ulcers without active bleeding. The event was determined by the investigator to be drug related).

- 6-month OA Studies (Table 37)

In both the 6-month and the 6-month to 86 week studies, the overall incidence and distribution by body system were comparable to the NSAID comparators (ibuprofen and diclofenac). There were more serious adverse experiences than in 6-week studies, consistent with the longer exposure and increased time of observation.

Incidences of serious clinical adverse events in 6-month studies were similar across all active-treatment groups: 29 (5.9%), 38 (4.3%), 25 (6.6%), 16 (4.2%), and 31 (6.2%) patients in the rofecoxib 12.5, 25, 50 mg QD, ibuprofen 800 mg TID, and diclofenac 50 mg TID groups, respectively. The incidence in placebo treated patients was 2.7% but this group had one-third less time on treatment and no direct comparisons can be made.

Similarly to the 6-week studies, the most frequent non-fatal serious adverse experiences were cardiovascular events (31 patients). A total of 28 of these 31 patients had risk factors for cardiovascular disease. There were five myocardial infarctions, four of them in patient taking rofecoxib 12.5 (two patients) or 25 mg QD (two patients)and one in a patient in the diclofenac group. There were five cerebrovascular accidents (CVA) and three transient ischemic attacks (TIA). Four of the CVA's were in the rofecoxib groups: one on 12.5 and three on 50 mg QD. Of the three TIA's two were on rofecoxib 25 and one was on rofecoxib 50 mg QD.

Three cardiovascular events were considered by the investigator to be possibly related to study drug: one transient ischemic attack (AN 5246 on rofecoxib 25 mg/ day), one episode of chest pain and dyspnea in a patient who was later diagnosed with SLE (AN161 on rofecoxib 50 mg/day) and one episode of chest pain (AN 7508 on diclofenac).

The second most common serious events were musculoskeletal and skin related events. (Nine hospitalizations for joint replacements and four for intervertebral disc displacement). Most of the other adverse experiences were fractures. Twelve of 13 adverse skin related experiences were basal cell carcinomas, and one was cellulitis.

Four serious GI related events were felt by the investigator to be drug related (all among patients on rofecoxib). Reports included one intestinal obstruction (AN 7507) and one "colitis" (AN 8292) in the rofecoxib 12.5 mg; one GI bleeding due to a duodenal ulcer (AN 5324) and one gastric ulcer complicated with GI obstruction (AN 5605) in the rofecoxib 25 mg group. No serious GI adverse events were considered by the investigator to be related to diclofenac. There were no serious GI adverse events in the ibuprofen group.

- 6-month to 86-weeks OA studies. (Table 37)

Again, the most common serious adverse events were of the cardiovascular system. Cardiovascular events in the rofecoxib groups (950 patients) included two cases of hypertension, 4 cases of ischemic-related events (one angina pectoris, one coronary artery vasospasm, one coronary artery occlusion, one coronary artery disease and one myocardial infarction), four cases of CHF, three cases of atrial fibrillation, three deep venous thrombosis and one cerebrovascular accident.

Cardiovascular events in the diclofenac group (115 patients) included one myocardial infarction, 2 cases of angina pectoris, one of chest pain and one of coronary artery disease. In the nabumetone group there were two cases of CHF and one of atrial fibrillation.

There were two cases of pancreatitis (one on rofecoxib 12.5 and one on rofecoxib 25 mg.) and four cases of urolithiasis (three in the rofecoxib 25 mg group and one in the diclofenac group).

Seven serious adverse events were considered by the investigator to be related to study drug. These included five patients on rofecoxib: AN 8163 (chest pain) in the 12.5 mg group; AN 2281(infectious gastroenteritis), AN 7985 and AN 4300 (two GI bleedings), and AN 5516 (urolithiasis) in the in 25 mg group. Two serious adverse events in diclofenac were felt by the investigator to be related to study drug: AN 2371(anemia) and AN 7993 (esophageal ulcer). No serious events were felt by the investigator to be related to ibuprofen or nabumetone.

> ***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.***

b) Most common clinical adverse events.

Adverse events with incidence higher than 1% in any treatment group are presented in Appendix 14. The most common adverse events were upper respiratory infection, sinusitis, diarrhea and headache.

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

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

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