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Douglas C Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20816
Tel (301) 594-5375, FAX (301) 594-5494

MEMORANDUM

FROM: Douglas C. Throckmorton, M.D., Medical Officer
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

THROUGH: Shaw Chen, M.D., Ph.D., Medical Team Leader
Robert Fenichel, M.D., Ph.D., Deputy Division Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

TO: Victoria Lutwak, Project Manager
James Witter, M.D., Ph.D., Medical Officer
John Hyde, M.D., Ph.D., Acting Deputy Division Director
Robert DeLap, M.D., Director, ODE V, and Acting Division Director
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products (DAAODP), HFD-550

SUBJECT: NDA 20-998
NAME OF DRUG: Celecoxib (SC-58635)
TRADE NAME: Celebrex
FORMULATION: Capsules for oral administration.

RELATED APPLICATIONS: None

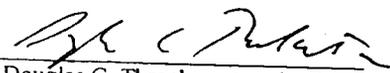
PROPOSED INDICATIONS: 1) Acute and chronic use in the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis; and
2) Management of pain.

SPONSOR: Searle

CONSULT RECEIVED: 7.15.98

DATE CONSULT COMPLETED: 12.10.98

ISSUES TO BE ADDRESSED: 1) Review of NDA 20-998 Cardiac and Renal Safety Database.
2) Review of three 'Renal' studies in NDA 20-998.


Douglas C. Throckmorton, M.D.

0.0 Overall Renal and Cardiac Safety Consultant Summary

General Summary

During the development of specific inhibitors of the type 2 isoform of cyclooxygenase (COX-2), it was hoped that they would provide selective anti-inflammatory efficacy without concomitant GI and renal toxicity. This was based on animal work that suggested that the GI system and kidneys did not express the COX-2 isoform. More recent work has demonstrated the clear presence of COX-2 in the kidney, both in the normal human and animal kidney and in patients with systemic lupus erythematosus. Work in animals has also suggested the up-regulation of COX-2 following volume contraction. These data suggest, at the very least, that the target of COX-2 inhibitors is present in the kidney, and they provide a plausible mechanism for any observed clinical renal toxicity. That this target (COX-2) may be increased during times of sodium- and water-depletion suggests a role for COX-2 in protecting renal hemodynamics. Whether this observation translates into an increased risk of nephrotoxicity in clinical states associated with potentially impaired renal perfusion, such as volume contraction, is not known at present.

Cardiac and renal safety was examined in both the short-term, controlled trials, and in the longer, open-label trial of patients with osteoarthritis/rheumatoid arthritis (OA/RA). Overall, 6376 patients were exposed to celecoxib during the short-term, controlled, North American trials in OA/RA. During the open-label trials, another 9822 patients received celecoxib. Of these, the large majority received the drug for <180 days. With regard to long-term exposure, 1809 OA/ RA patients received celecoxib for periods lasting for between 12 weeks and > 1 year in an open-label trial.

As part of the safety database, the sponsor collected adverse events related to both clinical and laboratory measurements. In addition, serial laboratory measurements were obtained from a subset of patients. Significantly, no measurements of acid-base balance database (e.g., serum bicarbonate, arterial pH) were performed as part of any trial in the NDA. With this exception, the database was sufficient to assess the clinically relevant renal and cardiac toxicities.

Cardiac Safety

The administration of celecoxib cannot be linked to any rare or unusual cardiac toxicities based on the available data. For some adverse events, including arrhythmias and overall cardiovascular mortality, the data are inadequate to either exclude or confirm an adverse effect of celecoxib.

With regard to **cardiovascular adverse events**, there is an association between celecoxib administration and **worsened hypertension** in susceptible individuals. This effect of celecoxib resembles that of other non-steroidal anti-inflammatory drugs (NSAIDs). There was also an association between celecoxib administration and the development of clinically significant **edema**, again similar to other NSAIDs.

Renal Safety

Three trials were performed on specific populations (elderly patients, patients with mild-to-moderate renal insufficiency, patients with volume contraction) to examine their renal responses to celecoxib. These trials examined the short-term effects of celecoxib on the excretion of prostaglandins, as well as a variety of other renal parameters. The trials enrolled small numbers of patients for short trial durations. Under the conditions of those trials, both celecoxib and the comparator NSAIDs inhibited prostaglandin PGE₂ and 6-keto-PGF₁-alpha by the kidney to more or less the same extent. Both had significant inhibitory effects on the excretion of these urinary prostaglandins when compared with placebo.

There was sufficient evidence to conclude that celecoxib has significant **renal effects**, as reflected in the pattern of lab abnormalities associated with celecoxib administration. This pattern includes a nominally-significant association between celecoxib and an increased incidence of several lab abnormalities: **hyperchloremia, hypophosphatemia, and elevated BUN in association with proteinuria**. These surrogates for renal toxicity suggest, but do not confirm, a link between celecoxib use and clinically relevant nephrotoxicity. Further, the incidence of the lab abnormalities occurred to a similar extent in both the celecoxib and the active control groups, suggesting that both celecoxib and the other NSAIDs have similar renal effects.

Within the limitations of the database, there is no evidence to suggest that celecoxib has unique renal toxicities not shared with other NSAIDs, or evidence of a renal toxicity caused by other NSAIDs that occurs at a significantly higher incidence rate with celecoxib. In the absence of bicarbonate data, an adverse effect of celecoxib on acid-base balance cannot be excluded, particularly in the context of the observed increase in hyperchloremia. The pattern of adverse events reported in both the controlled and the long-term trials is similar to that expected for NSAIDs. While there were no clear cases of celecoxib-induced renal failure requiring dialysis in the controlled database, there were several individuals taking celecoxib who were withdrawn from the long-term open-label trial because of renal adverse events, including acute renal failure (as well as edema and worsening hypertension). It remains to be determined whether severe renal injury will occur following celecoxib at the same rate that is seen with other NSAIDs.

While a through comparison of the renal effects of celecoxib and other NSAIDs has not been performed, the available data suggest that celecoxib resembles other NSAIDs in the majority of the renal effects examined in the NDA. Further, the available data suggest that the renal effects of celecoxib are clearly distinguished from placebo.

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1.0 Materials Utilized in Review

1.1 Materials from NDA

1. NDA 20-998, volumes: 1.1-1.3; 1.129; 1.134-1.43; 1.425-1.442.
2. NDA 20-998, submitted in CANDAs format.

1.2 Other Resources

No separate consultations, including outside experts or advisory committee proceedings, were obtained during this NDA review. Where appropriate, the results of the literature review are included in the Mechanisms of Action section below, and in the integrated Safety Summary (sections 5.1 and 5.2).

2.0 to 2.7 Background Information

The background information below is drawn from the sponsor's summary and from the published literature. Please see pertinent primary reviews for further details.

2.1 Chemistry

Celecoxib is a diarylsubstituted pyrazole and has the following structural formula: 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

2.2 Mechanism of Action

Celecoxib is a member of a novel class of anti-inflammatory and analgesic agents known as specific cyclooxygenase type 2 (COX-2) inhibitors. Celecoxib causes persistent inhibition of COX-2 through an interaction with a distinct region of the active site. Therapeutic concentrations of celecoxib maximally inhibit the formation of prostaglandins by COX-2. In animal models, inhibition of COX-2 has been observed to have anti-inflammatory, analgesic, antipyretic and anti-proliferative effects. In animals, these effects of celecoxib occur at concentrations that inhibit COX-2 *in vitro*. At therapeutic concentrations, the sponsor reports that celecoxib does not inhibit the constitutive isoenzyme (COX-1) which functions to produce prostaglandins involved in maintenance of the GI mucosal barrier, platelet aggregation and renal function.

There is limited information about the role that COX-2 plays in the kidney. In rats and dogs, COX-2 is constitutively expressed in the macula densa and adjacent epithelial cells of the cortical collecting duct (references 1,2). The authors of these papers speculate that COX-2 is critical for the response to volume-contraction, perhaps by regulating renin release from the macula densa. It has also been reported that COX-2 is not normally present in adult human kidneys, but is up-regulated in lupus nephritis (reference 3).

2.3 Pharmacokinetics/ pharmacology/ pharmacodynamics

Pharmacokinetics: The pharmacokinetics of celecoxib have been evaluated in approximately 1500 individuals. In addition to healthy, young and elderly volunteers (male and female), pharmacokinetic measurements have been done in patients and also in special populations including individuals with hepatic or renal impairment. The table below summarizes the pharmacokinetics of celecoxib (per the sponsor).

Table 2.3.1 Summary of single dose disposition kinetics of celecoxib in healthy subjects^a.

Parameter	Mean (% CV)
C _{max} , (ng/ ml)	598 (54)
T _{max} , (hr)	3.42 (45)
AUC ₍₄₈₎ , (ng/ ml)* hr	6270 (30)
AUC _(inf) , (ng/ ml)* hr	6694 (30)
T _{1/2} , (hr)	11.7 (39)
V _Z /F, (L/ 70 kg)	533 (51)
CL/ F, (L/ hr/ 70 kg)	31.7 (34)
Relative bioavailability, (%)	99 (95- 104)

a. Data from proposed labeling, NDA 20-998 vol. 1.1

Pre-clinical renal pharmacology and pharmacodynamics:

Celecoxib was tested for its effect on urinary volume and electrolyte excretion in rats at oral doses from 5 to 500 mg/kg. Celecoxib decreased urinary volume 28 to 43% between 15 and 500 mg/kg with a plateau in effect from 50 to 500 mg/kg. Sodium excretion was decreased with celecoxib doses from 50 to 500 mg/kg by 17 to 36% with a plateau in effect from 150 to 500 mg/kg. Chloride excretion was decreased by celecoxib doses from 50 to 500 mg/kg by 16 to 35% with a plateau in effect from 150 to 500 mg/kg. Urinary osmolarity was increased by celecoxib doses of 15 to 500 mg/kg by 16 to 38% with a plateau in effect from 150 to 500 mg/kg.

In a high-dose study, celecoxib was administered 600 mg/kg/day to male rats for 7 days. In this study, celecoxib had no effect on urinary volume or urinary excretion of PGE₂. Plasma levels of celecoxib reached 6.99 ng/ml on day 7 at 5 h after dosing. As a control, indomethacin (4 mg/kg/day) lowered PGE₂ urinary levels and volume only on day 3.

2.4 Metabolism

Metabolism: Celecoxib metabolism is predominantly mediated via cytochrome P₄₅₀ 2C9 in the liver. The methyl group of celecoxib is hydroxylated to a primary alcohol that is further metabolized to a carboxylic acid. A minor amount of the carboxylic acid metabolite is conjugated to glucuronic acid to form the 1-O-glucuronide. The metabolites are inactive as COX-1 or COX-2 inhibitors. *In vitro* studies indicate that celecoxib is not an inhibitor of cytochromes P₄₅₀ 2C9, 2C19 or 3A4, and though not a substrate, it is a relatively weak inhibitor of cytochrome P₄₅₀ 2D6. However, plasma concentrations of celecoxib achieved in humans, at the recommended doses, are not expected to substantially inhibit the metabolism of other drugs that are metabolized via the 2D6 isozyme. Clinical data to confirm this expectation are not available.

Excretion: Celecoxib is eliminated predominantly by hepatic metabolism with no detectable unchanged drug recovered in the urine. Celecoxib is excreted as the acid metabolite predominantly in the feces (approximately 54% of the administered dose) and to a lesser extent in the urine (approximately 18% of the administered dose).

2.5.1 Renal Toxicology

1) 2-week administration to mice

Lesions consistent with test-article associated renal injury were found in three males (95S0745, 95S0746, and 95S0747) and four females (95S0754, 95S0755, 95S0756, and 95S0762) from the 1000 mg/kg/day dosage group. All seven animals demonstrated a nephropathy characterized by focal degeneration of renal tubules with regeneration, epithelial basophilia, intraluminal casts (cellular or hyaline) and a minimal mononuclear cell interstitial infiltrate. In all animals the lesion was slight to mild except for one 1000 female (95S0754) where it involved the cranial 1/3 of the left kidney (corresponding to a macroscopic lesion). The sponsor noted that while these lesions are sometimes seen in aged mice, they would not be expected in mice this age.

One incidence of renal papillary necrosis (moderate, Grade 3 of 5) was reported in a male receiving 1000 mg/kg/day.

2) 4-week administration to dogs

No histologic damage was reported in the 25 mg/kg dose group. Slight to moderate acute renal papillary necrosis was diagnosed in four animals including one male given 50 mg/kg, two females given 100 mg/kg, and one male given 250 mg/kg. Notable was the slight acute unilateral papillary necrosis that was seen in one female in the 100 mg/kg reversal group. Per the sponsor, later studies using lower-doses of celecoxib did not demonstrate any histologic evidence of renal toxicity.

Based on their review of both the low- and high-dose exposure data across species, the sponsor concluded that there was no significant renal papillary necrosis seen in the animal models, and that the 'absence of renal papillary necrosis in chronic rodent studies' suggested that celecoxib 'is different from NSAIDs.'

2.5.2 Cardiac Toxicology

1) Acute infusion to guinea pigs

The cardiopulmonary effects of celecoxib were examined in an acute guinea pig model. The only effect, per the sponsor, was a small but significant increase in systolic blood pressure.

2) Acute administration to anesthetized dogs

The only significant effect noted in this model was an increase in left-ventricular end-diastolic pressures seen at the higher doses in 2/4 dogs. No effect on blood pressure or other vital signs was detected.

2.6 Proposed Renal and Cardiac Labeling

Below are sections of the proposed label that pertain to celecoxib renal efficacy and/or safety. The statements for each section are per the sponsor, and come from the proposed labeling section of the NDA. A discussion of the appropriateness of each of the statements will be included in the Integrated Safety Summary (section 5.3 and 5.4).

Dosing: The maximum proposed dose of celecoxib 400 mg per day in divided doses.

Pharmacodynamics: Celecoxib causes persistent inhibition of COX-2 through a novel interaction with a distinct region of the active site. Therapeutic concentrations of celecoxib maximally inhibit the formation of prostaglandins by COX-2. At therapeutic concentrations celecoxib does not inhibit the constitutive isoenzyme (COX-1) which functions to produce prostaglandins involved in maintenance of the GI mucosal barrier, platelet aggregation and renal function.

Pharmacokinetics: The pharmacokinetics of Celebra have been evaluated in approximately 1500 individuals. In addition to healthy, young and elderly volunteers (male and female), pharmacokinetic measurements have been done in patients and also in special populations including individuals with hepatic or renal impairment.

Excretion: Celecoxib is eliminated predominantly by hepatic metabolism with no detectable unchanged drug recovered in the urine.

Special studies (Safety)

Renal: Celebra has no deleterious effects on renal function. Administration of Celebra at doses of 200 and 400 mg BID for periods of 7- 10 days was studied in elderly subjects and patients with moderate renal impairment.

Dosage Adjustment in Special Populations

Renal insufficiency: Because celecoxib is predominantly metabolized by the liver and none of the metabolites are pharmacologically active, no dosage adjustment is necessary in patients with mild to moderate renal insufficiency. In elderly volunteers with age related reductions in GFR ($< 65 \text{ ml/min/1.73 m}^2$) and in patients with moderate renal insufficiency (GFR 35- 60 ml/min/1.73 m²), celecoxib pharmacokinetics were comparable to those seen in patients with normal renal function. No significant relationship was found between serum creatinine and estimated creatinine clearance and celecoxib clearance. Patients with severe renal insufficiency have not been studied and therefore should use the lowest effective dose.

Precautions

General

Because Celebra has no effect on platelet function, it should not be used for cardiovascular prophylaxis.

Renal effects: The effect of Celebra in advanced renal disease (GFR $< 40 \text{ ml/min/1.73 m}^2$) has not been studied. No prospective studies have been conducted in patients with considerable dehydration, advanced renal disease, congestive heart failure or liver dysfunction.

Use in Elderly: In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers.

ACE-Inhibitors and Diuretics

Although prospective studies of Celebra with ACE inhibitors and diuretics have not been conducted, no increased incidence of adverse reactions indicative of elevations in blood pressure were seen in clinical trials in which arthritis patients were taking Celebra concurrently with ACE inhibitors, or diuretics. No increased incidence of adverse reactions indicative of sodium retention or renal impairment were seen in clinical trials in patients taking Celebra concurrently with diuretics.

Aspirin:

Celebra has been administered to patients taking aspirin up to 325 mg per day. Low doses of aspirin have been associated with ulcers. Thus concomitant use of Celebra with aspirin may result in an increased rate of GI ulceration compared to when Celebra is used alone.

3.0 Description of Clinical Data Sources

3.1 Primary Source Data

A total of 29 clinical pharmacology and 22 phase II/III clinical efficacy trials were performed as part of the celecoxib development. Of these, 13 clinical trials were performed to compare celecoxib with other NSAIDs. Three of these latter studies focused on the renal effects of celecoxib: study 010 (Renal effects in the elderly); study 033 (Na⁺/volume depletion and renal effects); and study 036 (Renal effects in chronic renal insufficiency). These three trials will be examined individually.

In total, the safety database used for this consult includes 13,072 individuals enrolled in clinical trials. More than 75% of these individuals had either osteoarthritis (OA) or rheumatoid arthritis (RA), and enrolled in trials of \geq 2 weeks duration.

3.1.1 Study Type and Design/Patient Enumeration

3.1.2 Demographics

The first table summarizes the subject exposure to celecoxib in the entire database.

Table 3.1.2.1 Summary of Celecoxib-treated subjects in the NDA 20-998 database^a.

Study Design	# Of Treated Subjects	# of Unique Subjects ^b
Phase I: Single Dose	294	251
Phase I: Multiple Dose	398	270
Phase I: Drug Interactions	260	131
Phase I: Hepatic	48	48
Phase I: Renal	23	23
Arthritis: OA	4280	4151
Arthritis: RA	2096	2086
Arthritis: Long-term Open-label	4499	1757
Analgesia: Dental pain	531	529
Analgesia: Surgical pain	217	217
Combined Studies	12646	9463

a. Data from NDA Integrated Summary of Safety Information, table 2.11.

b. Individuals who received celecoxib as part of more than one trial are counted only once.

3.1.3 Extent of Exposure (dose/duration)

Dose Exposure to Celecoxib

The next table summarizes the celecoxib exposure according to the dose of celecoxib for all studies in the NDA.

Table 3.1.3.1 Summary of celecoxib exposure by dose from NDA 20-998^a.

Treatment and Dose	Treated Subjects	Unique Treated Subjects
Celecoxib Single Dose (5-1200 mg)	825	780
Celecoxib Multi-Dose		
5-50 mg	959	948
100 mg	4872	3261
200 mg per day	564	500
200 mg	4562	3272
400 mg	721	665
600 - 1200 mg	20	20
Celecoxib +Other Drug	123	17
Total	12646	9463
Comparator Agents		
Placebo	2450	1354
Active Controls	3343	2255
Total	5793	3609
Overall Total	18439	13072

a. Data from NDA 20-998, Integrated Summary of Safety, Text Table 5.

3.1.3 Extent of Exposure (dose/duration) (cont)

Duration Exposure to Celecoxib

The chronic exposure data comes from the trials in osteoarthritis (OA) or rheumatoid arthritis (RA). This will be the database used primarily for the assessment of renal and cardiac safety. The table below summarizes the duration of patient exposure in the OA/ RA database, broken into three categories: 0-6 weeks; 6 weeks to 6 months; and greater than 6 months. Note that there are very few subjects who received celecoxib with long-term (>180 days) exposure to celecoxib in a controlled trial (n=39). A larger number received celecoxib in open-label trials for >180 days (n=1809).

Table 3.1.3.2 Duration of arthritis patient exposed to celecoxib in the NDA 20-998 database^a.

	25-50 mg	100 mg	200 mg	300 mg	400 mg	Total ^b
OA-RA Controlled Trials						
1-42 days	462	888	818	0	308	2476
43-180 days	481	1237	1836	0	307	3861
>180 days	0	0	39	0	0	39
OA-RA Uncontrolled (Open-Label) Trials						
1-42 days	110	1689	1527	768	200	4294
43-180 days	310	970	1509	451	489	3729
>180 days	0	236	941	222	410	1809
Total	1363	5020	6670	1441	1714	16208

a. Data from NDA 20-998, vol. 1.426, Table 3.4

b. There were 18 additional patients who received other doses (i.e., 200 mg in am, 300 mg in pm). These are included in the safety review but not this table.

The sponsor also summarized exposure to celecoxib in patient-years of exposure for all subjects in the arthritis trials. The results are shown below.

Table 3.1.3.3 Duration of exposure to celecoxib, by patient-years, in the NDA 20-998 database^a.

	50 mg	100 mg	200 mg qD	200 mg BID	300 mg	400 mg	Any Dose ^b
OA-RA Controlled Trials	116	289	47	466	0	87	1020
OA-RA Uncontrolled (Open-Label) Trials	75	518	0	1271	340	465	2672
OA-RA Controlled & Uncontrolled Trials	117	680	47	1567	340	499	3267

a. Data from NDA 20-998, Integrated Summary of Safety, Table 4.3. Patients are counted only once per treatment group.

b. There were 18 additional patients who received other doses (i.e., 200 mg in am, 300 mg in pm). These are included in the safety review but not this table.

The demographics of the subjects enrolled in the North American arthritis trials are summarized below.

Table 3.1.3.4 Demographics of the North American arthritis trials in NDA 20-998^a.

Demographic	Placebo N=1864	Celecoxib N=5704	Active Controls N=2098
Age			
Mean	60.0	59.5	58.8
>64	731 (39.2%)	2117 (37.1%)	737 (35.1%)
Ethnicity			
White	1629 (87.4%)	4844 (84.9%)	1792 (85.4%)
Black	156 (8.4%)	580 (10.2%)	216 (10.3%)
Hispanic	67 (3.6%)	219 (3.8%)	78 (3.7%)
Asian	4 (0.2%)	34 (0.6%)	6 (0.3%)
Other	8 (0.4%)	27 (0.5%)	6 (0.3%)
Gender			
Female	1324 (71.0%)	3986 (69.9%)	1427 (68.0%)
Male	540 (29.0%)	1718 (30.1%)	671 (32.0%)

a. Data from NDA Integrated Safety Summary, table 6.1.

3.1.3 Extent of Exposure (dose/duration) (cont)

The sponsor collected information on the past medical histories of the subjects enrolled in the trials as well. Below are the incidences of relevant cardiac and renal medical history (arranged according to ICD-9 codes) in the North American controlled trials. Unlisted ICD-9 codes occurred at <1.0% or were considered non-significant for purposes of this review. Overall, a significant fraction of the subjects had hypertension. A much smaller % had a history of significant cardiac disease or renal disease. No information about smoking history is available.

Table 3.1.3.5 Significant cardiac and renal past medical history in the celecoxib North American controlled trials^a.

	Placebo N=1864 ^b	Celecoxib 25- 400 mg N=5704 ^c	Active Controls N=2098 ^d
Cardiovascular Disease			
Angina Pectoris	57 (3.1%)	194 (3.4%)	75 (3.6%)
Coronary Atherosclerosis	70 (3.8%)	201 (3.5%)	82 (3.9%)
Congestive Heart Failure	24 (1.3%)	63 (1.1%)	25 (1.2%)
Hypertension (not otherwise specified)	732 (39.3%)	2172 (38.1%)	749 (35.7%)
CABG	31 (1.7%)	118 (2.1%)	39 (1.8%)
Myocardial Infarction (not otherwise specified)	54 (2.9%)	167 (2.9%)	74 (3.5%)
Endocrine Disease			
Diabetes Type I (uncomplicated)	26 (1.4%)	89 (1.5%)	34 (1.6%)
Diabetes Type II (uncomplicated)	114 (6.1%)	408 (7.2%)	156 (7.4%)
Hypothyroidism	234 (12.6%)	659 (11.6%)	241 (11.5%)
Hyperlipidemia	108 (5.8%)	376 (6.6%)	137 (6.5%)
Obesity	131 (7.0%)	389 (6.8%)	148 (7.1%)
Renal/ GU Disease			
Renal calculus	64 (3.4%)	206 (3.6%)	93 (4.4%)
Hematuria	29 (1.6%)	65 (1.1%)	17 (0.8%)
UTI	95 (5.1%)	231 (4.0%)	76 (3.6%)

a. Data from NDA Integrated Safety Summary, Appendix 8.2. The database used includes studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087. Collected ICD-9 codes were used to calculate incidence rates for each group.

Regarding the demographics of the subjects in the long-term, open-label study, these will be similar to those in the table above. This is because all of the subjects in the open-label trial first enrolled (and completed) one of the shorter trials prior to entry into the open-label, long-term trial.

The renal effects of celecoxib were studied specifically in three small trials and as part of the overall safety database. The three 'Renal Effects' trials are reviewed in section 4.0. Note that the longest period of exposure to study drug was 7 days in these three trials.

Table 3.1.3.6 Summary of 'Renal Effects' Trials in the NDA 20-998 database.

Study #	Short Title	Duration of Exposure to Study Drug	# of Control Subjects ^a	# of Celecoxib Subjects
010	Renal Effects in the Elderly	10 Days	27	26
033	Na ⁺ /Volume Depletion and Renal Effect	7 Days	21 ^a	21
036	Renal Effects in Chronic Renal Insufficiency	7 Days	52 ^a	23

a. Includes subjects who received active controls.

3.1.4 Renal Data Collected in the NDA Database

Renal adverse events were collected both during the 3 trials summarized above, and as part of the overall adverse event reporting for the rest of the clinical program. In the three 'Renal Effects' trials specific measures of renal function were measured (e.g., urine prostaglandin excretion). These will be discussed in the trial summaries below. For the clinical trials as a whole, adverse events were identified either through periodic meetings between the subjects and investigators, or through the use of subject diaries. Serious adverse events that were identified were transmitted to the sponsor immediately.

For evaluation of clinical laboratory results, the sponsor set upper and lower limits representing values of potential clinical relevance, along with cutoff values considered to represent lower and upper extremes. The table below shows the relevant boundaries for the renal laboratory adverse events. Note that no extreme value for bicarbonate was established. In response to this reviewer's request, the sponsor stated that... 'we have checked the clinical studies in our NDA 20-998 and can confirm that there are no studies which tested for bicarbonate either by gas determination or in serum.' (Letter, 8.7.98).

Table 3.1.4.1 Mid-range and extreme value limits for evaluation of clinical lab results in NDA 20-998^a.

Lab Test	Lower Extreme	Lower Mid-Range Limit	Higher Mid-Range Limit	Upper Extreme
Serum Measurements				
Creatinine	N/A	N/A	176.8 µmol/L (=2 mg/dl)	265.2 µmol/L (=3 mg/dl)
BUN	N/A	N/A	9.3 mmol/L (=27 mg/dl)	14.3 mmol/L (=42 mg/dl)
Sodium	120 mmol/L	135 mmol/L	140 mmol/L	160 mmol/L
Potassium	2.0 mmol/L	3.5 mmol/L	5.0 mmol/L	6.0 mmol/L
Chloride	75 mmol/L	90 mmol/L	110 mmol/L	130 mmol/L
Calcium	>15% below Baseline, or <1.7 mmol/L	2.0 mmol/L	2.74 mmol/L	3.74 mmol/L
Inorganic phosphorus	0.32 mmol/L	0.97 mmol/L	1.61 mmol/L	2.42 mmol/L
Urinalysis				
Protein	N/A	N/A	Trace	1+ (300 mg/24h)
Blood	N/A	N/A	Trace	1+
Glucose	N/A	N/A	Trace	1+ (1 g/24h)
pH	N/A	4	8	8.5
Specific gravity	N/A	1.003	1.030	1.040
RBC	N/A	N/A	5/hpf	10/hpf
WBC	N/A	N/A	10/hpf	20/hpf
Ketones	N/A	N/A	Trace	1+
Urine bilirubin	N/A	N/A	Trace	1+

a. Data from NDA 20-998, Integrated Summary of Safety, Text Table 3.

3.1.5 Cardiac Data Collected in the NDA Database

While no trials specifically addressed the question of cardiovascular effects of celecoxib, certain elements of cardiovascular safety were collected as part of the assessment of each subject: blood pressure; heart rate; weight. The occurrence of lab abnormalities for creatine phosphokinase was also collected. As part of the safety database, other cardiovascular adverse events (AEs) were collected, including the occurrence of: cardiac ischemia, arrhythmias, strokes, and hypertension.

3.2 Data from Secondary Sources/ Published Literature

Aside from the published literature, no secondary sources of data were used in this consult. Two approaches were used to identify relevant published literature relevant to the current submission.

First, this reviewer conducted an independent literature review, through a keyword search of Medline. Second, the sponsor has provided a literature review, which was cross-referenced with the above reviews to assure completeness. The cut-off for consideration of articles in this NDA was approximately January of 1998. This literature review has been incorporated into the background section of this introduction, and into the integrated safety summary where appropriate. References appear at the end of the Integrated Renal/ Cardiac Safety Summary, section 5.3.

3.3.1 Comment on Adequacy of Clinical Experience

The database includes a total of 9463 subjects in the clinical database who were exposed to celecoxib. With regard to the number of subjects exposed, a total of 7718/ 9463 subjects (82%) received celecoxib at a dose of ≥ 100 mg per day (dosed as 50 mg BID). Without regard to the duration of exposure, this yields a 95% likelihood of detecting at least one occurrence of adverse events occurring at a rate of between 1/1000 and 1/10,000. Less information, obviously, will be available regarding the incidence rates for adverse events.

With regard to the duration of exposure, very few subjects (39) in the arthritis trials were exposed to celecoxib for >6 months as part of a controlled trial (active or placebo). A larger number (1809) were exposed for >6 months as part of open-label arthritis studies. As a consequence of this, the detection of common AEs that result from chronic exposure (i.e., myocardial infarction, elevated blood pressure), will simply be impossible, since no comparison group is available. More uncommon severe AEs (i.e., vasculitis, pancytopenia) may be detected as occurring in the open-label data, although their incidence will be impossible to determine.

3.3.2 Comment on Data Quality and Completeness

Specifics regarding the completeness of the database for NDA 20-998 will be made during the reviews of the three 'renal' trials, and in the combined Renal/ Cardiac Safety Review (section 4.0 to 4.2 below).

Regarding overall patient exposure, the ability to detect an effect of long-term exposure to celecoxib on AEs is limited by the lack of control data beyond 12 weeks. Inferences regarding long-term toxicity must therefore be drawn from the longer-term open-label data.

Regarding lab data collection, follow-up for abnormal laboratories was dependent on the individual investigators.

Regarding the renal safety review, no information about the acid-base status of any individuals was collected as part of the NDA (i.e., no serum bicarbonates, no arterial pH measurements). This concern was conveyed to the sponsor, and will be discussed further as part of the Safety review.

Regarding cardiac safety review, no information on ECG abnormalities was routinely collected or analyzed.

The Case Report Forms were submitted for all subjects who withdrew from the studies, including both medical and non-medical drop-outs. These were submitted as PDF files on optical discs, and are sufficient for review.

The datasets were submitted both in SAS and hardcopy.

In summary, the data quality and completeness is acceptable for a medical review with emphasis on the renal and cardiac safety. Specific problems regarding the adequacy of the data are noted at appropriate points in the review document.

Discontinuations associated with Adverse Events (AEs)

The next table summarizes the subjects who were withdrawn from study drug prematurely due to one or more adverse events related to the cardiac or renal systems.

Table 5.1.6.3 Cardiovascular adverse events leading to subject discontinuation collected in the North American OA/RA trials^a.

Body System/ AE	Placebo N=1864	Celecoxib 50-400 mg BID N=5704	Active Control N=2098
Total # with AEs leading to discontinuation	114 (6.1%)	298 (7.0%)	203 (9.7%)
Hypertension ^b	0 (0%)	6 (0.1%)	1 (<0.1%)
Hypotension, includes postural	0 (0%)	1 (<0.1%)	2 (<0.1%)
Edema, peripheral	1 (<0.1%)	4 (<0.1%)	1 (<0.1%)
Edema, facial	3 (0.2%)	7 (0.1%)	2 (0.1%)
Edema, Generalized	0 (0%)	1 (<0.1%)	2 (0.1%)
Arrhythmia ^c	1 (<0.1%)	0 (0.16%)	3 (0.14%)
Arteritis/ Vasculitis	0 (0%)	1 (<0.1%)	0 (0%)
Angina ^d	2 (0.1%)	2 (<0.1%)	1 (<0.1%)
Myocardial infarction	2 (0.1%)	6 (0.1%)	2 (0.1%)

a. Data from Integrated Safety Summary, Appendix table 6.4.

b. Includes hypertension, aggravated hypertension.

c. Includes 'arrhythmia', atrial arrhythmia, atrial fibrillation, palpitation, tachycardia, and supraventricular tachycardia.

d. Includes angina pectoris, aggravated angina pectoris and unstable angina.

Table 5.1.6.4 Renal adverse events leading to subject discontinuation collected in the North American OA/RA trials^a.

Body System/ AE	Placebo N=1864	Celecoxib 50-400 mg BID N=5704	Active Control N=2098
Total # with AEs leading to discontinuation	114 (6.1%)	298 (7.0%)	203 (9.7%)
Uremia	0 (0%)	1 (<0.1%)	0 (0%)
Abnormal renal function	1 (<0.1%)	0 (0%)	0 (0%)
Renal calculus	1 (<0.1%)	1 (<0.1%)	0 (0%)

a. Data from Integrated Safety Summary, Appendix table 6.4.

Table 5.1.6.5 Cardiovascular adverse events leading to subject discontinuation, collected in the long-term, open-label trial^a. Shown according to the date of last celecoxib dose.

Adverse Event	1-90 Days	91-180	181-270	271-360	361-450	451-540
# of Subjects Total	4499	3540	2373	1576	970	294
Total # with AEs leading to discontinuation	147 (3.3%)	99 (2.8%)	34 (1.4%)	21 (1.3%)	6 (0.6%)	2 (0.7%)
Hypertension ^b	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)
Edema, generalized	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Edema, facial	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Edema, peripheral	4 (0.1%)	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)
Fibrillation, Atrial	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	0 (0%)	0 (0%)
Palpitation	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fibrillation, Ventricular	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cardiac Failure	1 (<0.1%)	1 (<0.1%)	3 (0.1%)	1 (<0.1%)	0 (0%)	0 (0%)
Unstable Angina ^d	0 (0%)	2 (0.1%)	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)
Myocardial Infarction ^c	4 (0.1%)	2 (0.1%)	1 (<0.1%)	1 (<0.1%)	0 (0%)	0 (0%)
Arteritis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

a. Data from Integrated Safety Summary, Appendix table 9.6.

b. Includes hypertension, aggravated hypertension.

c. Includes coronary thrombosis.

d. Includes 'angina pectoris.'

Table 5.1.6.6 Renal adverse events leading to subject discontinuation, collected in the long-term, open-label trial^a. Shown according to the date of last celecoxib dose^a.

Adverse Event	1-90 Days	91-180	181-270	271-360	361-450	451-540
# of Subjects Total	4499	3540	2373	1576	970	294
Total # with AEs leading to D/C	147 (3.3%)	99 (2.8%)	34 (1.4%)	21 (1.3%)	6 (0.6%)	2 (0.7%)
BUN Increased	1 (<0.1%)	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Acute Renal Failure	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

a. Data from Integrated Safety Summary, Appendix table 9.6. Other events, including albuminuria, bladder carcinoma, hematuria, and UTI, led to discontinuation of single subjects in the database.

Per the sponsor, twenty-five (25) patients were withdrawn from the controlled OA/RA trial due to renal adverse events. A total of four patients (0.2%) withdrew from placebo treatment. For the celecoxib 50 mg BID to 400 mg BID treatment groups combined, 16 patients (0.3%) withdrew as a result of an adverse event associated with renal function. In the active control group, five patients (0.2%) withdrew from treatment for a renal adverse event. Note that the incidence of withdrawal for hypertension and for edema were higher in both the celecoxib and active control groups than in the placebo group. Time constraints precluded review of the individual Case Report Forms.

Table 5.1.6.7 Patients in the controlled OA/RA trials withdrawn due to renal adverse events^a.

Treatment Group/ Patient #	Preferred Term for AE
Placebo	
020-880	Hematuria
021-0445	Edema, Peripheral
022-0345	Renal Calculus
060-0441	Renal Function, Abnormal
Celecoxib 50-400 mg	
054-0501	Creatinine Increased
020-0123	Hypertension
054-0758	Peripheral Edema
060-0447	Peripheral Edema
087-0243	Peripheral Edema
020-0294	Hypertension
020-1147	Hypertension, Aggravated
021-1340	Creatinine Increased
054-0153	Hypertension
054-1396	Hypertension, Aggravated
071-2008	Hypertension, Aggravated
071-3061	Renal Calculus
012-0483	Generalized Edema
047-0030	Uremia
047-0320	Hyperkalemia
Active Control	
023-0671	Generalized Edema
023-0827	Generalized Edema
071-1250	Creatinine Increased
071-1310	Peripheral Edema
071-1737	Hypertension

a. Data from sponsor at reviewer's request.

Per the sponsor, twenty-five (39) patients were withdrawn from the long-term open-label trial due to renal and/or cardiac adverse events. Within this list, 22 subjects, listed below, were withdrawn for renal AEs. The remaining 17 had cardiac AEs, including 6 with cerebrovascular accidents, 8 with acute myocardial infarctions, and 3 with angina pectoris.

Table 5.1.6.7 Patients in the long-term OA/RA trial (024) withdrawn due to renal adverse events^a.

Celecoxib Dose ^b / Patient #	Final Dose	Adverse Event	Days on Celecoxib
<i>Celecoxib 100 mg</i>			
054-0153	100	Hypertension	N/A
021-0033	100	Increased BUN	16, ongoing
021-1043	100	Increased BUN	133, ongoing at day 138
		Increased Creatinine	
		Hyperkalemia	
020-0213	100	Edema, ankle and peripheral	93
020-0313	100	Edema, peripheral and lower extremity	285, ongoing
054-0854	100	Renal insufficiency	76, ongoing
		Increased Creatinine	
054-0589	100	Edema, peripheral	51, lasted 6 days
013-0285	100	Edema, generalized	4, ongoing
<i>Celecoxib 200 mg</i>			
020-0123	200	Hypertension	4, ongoing at day 465
022-0975	200	Acute Renal Failure	127, ongoing
021-0946	200	Edema, peripheral and lower extremity	34, ongoing at day 37
021-0883	200	Edema, peripheral and lower extremity	32
022-0114	200	Edema, facial	3
020-1071	200	Proteinuria, Albuminuria	5, ongoing at day 118
023-0393	200	Hematuria	177, ongoing
054-0595	200	Edema, peripheral and lower extremity	85, ongoing
054-0629	200	Hypertension	42, ongoing
<i>Celecoxib 300 mg</i>			
023-1173	300	Edema, facial	N/A
023-0671	300	'Urine abnormal' & 'Urine smells'	N/A, ongoing at day 310
		Edema, generalized	
<i>Celecoxib 400 mg</i>			
012-0090	400	Azotemia & Increased Creatinine	455, lasted 34 days
022-0313	400	Increased Creatinine	167, lasted 17 days
023-0051	400	Hypertension, Aggravated	374, ongoing

a. Data from sponsor at reviewer's request submitted 11.3.98.

5.2 Integrated Summary of Renal and Cardiac Safety

This section will summarize the critical renal and cardiac safety issues identified by this reviewer. Each will be discussed in turn, followed by an opinion regarding the association between celecoxib administration and each particular adverse event. An adverse event has been included either because, in the opinion of this reviewer, it is significantly more or less common in the celecoxib-treated patients when compared with the placebo group, or because it is a critical aspect of usual cardiac/renal safety review. Those adverse events that are not listed in this section are interpreted as either occurring too rarely to determine their association with celecoxib use or occurred with no evidence of specific association with celecoxib use.

In reviewing the database summarized above, this reviewer was careful to examine the data for evidence of events occurring more frequently in the placebo group relative to celecoxib, in addition to searching for events linked to celecoxib use. This is important so as to avoid the bias potentially present in any analysis that includes multiple analyses such as the safety review. It is also important to remember that the use of statistics to examine the incidence of rare and unusual events in a safety database is flawed with the same difficulties inherent to multiple looks. The intent of the following sections is to look for trends suggesting an increased incidence of a given adverse event, based on multiple lines of (indirect) evidence. This is, of course, the nature of a safety review.

Before listing the adverse renal and cardiac safety events, the limitations of the available safety database need to be reviewed.

5.2.1 Limitation of NDA Dataset for Detecting Renal and Cardiovascular AEs

There are two limiting factors that an NDA places on the detection of renal and cardiac adverse events (AEs): 1) the extent of patient exposure in both controlled and uncontrolled trials; and 2) the potential absence of relevant data.

Patient Exposure

Overall, 6376 patients were exposed to celecoxib during the short-term, controlled, North American trials in OA/RA. During the open-label trials, another 9822 patients received celecoxib. Of these, the large majority received the drug for <180 days. Long-term, open-label exposure data (>180 days) was collected for 1809 patients, (see Table 3.1.3.2).

The number of patient-years of exposure puts absolute limits on detecting and characterizing the renal and cardiac safety of celecoxib. Using the number 6376, and not taking into account the duration of exposure, we can estimate a 95% likelihood of detecting at least one occurrence of adverse events occurring at a rate of between 1/1000 and 1/2500. Less information, obviously, will be available regarding the relative rates for adverse events (i.e., celecoxib vs. placebo). Comparative rates between celecoxib and placebo (or active control) will be limited by the fact that the placebo-controlled trials were limited to 12 weeks or less of exposure. Using 1809 as the number of patients in the long-term exposure data yields a 95% likelihood of detecting at least one occurrence of an adverse event related to chronic exposure (>12 weeks) that occurs at a frequency of approximately 1/600. In terms of known renal toxicities of NSAIDs, such database would likely detect the occurrence of fluid and electrolyte disturbances (especially edema and worsened hypertension), which is the most common 'renal' toxicity of NSAIDs. It is less likely to detect other rare toxicities that occur at a frequency <1/1000 (nephrotic syndrome, papillary necrosis). The incidence of 'acute renal failure' due to NSAIDs is difficult to estimate, but if it occurs at a frequency of 1/500 to 1/1000, then we might expect the celecoxib database to detect at least one such event.

It is also relevant to discuss the uncontrolled aspect of the long-term safety database. As shown in table 5.03.1, the chronic exposure data is almost exclusively uncontrolled and open-label. Some adverse events occur predominately after long periods of exposure to study drug (>180 days). For example, the effect of a study drug on cardiac mortality would likely require long periods of exposure to become manifest. Without a direct comparator group within the long-term trials, the reviewer is forced to make assumptions about the expected rate of a given adverse event occurring in an untreated population at large from other sources (i.e., publication of other trials, epidemiology data). The approach limits the power to strongly associate such an adverse event with celecoxib with any confidence. Obviously, if detection of adverse mortality effects is difficult, it also be more difficult to discern associations between study drug and less severe adverse events in an uncontrolled database. For these adverse events (i.e., liver function abnormalities, acute renal failure) weight will of necessity be given to withdrawals due to a given adverse event, SAEs, and other indirect markers of incidence.

Data Collection

There is obviously a trade-off between the desire on the part of the FDA for complete safety information and the practicalities of performing large clinical trials. For the development of celecoxib, the sponsor did not collect serum bicarbonate data, normally a routine part of serum electrolytes. One possible explanation was the use of central lab facilities, which precludes the accurate measurement of HCO₃, unless labor-intensive steps are taken. As is clear from the above analyses, this omission, in association with the significantly increased incidence of hyperchloremia, forces the use of other, less clear-cut, markers for acid-base balance. Ultimately, this decision means that the data needed to resolve questions related to the effect of celecoxib on acid-base balance will simply not be available.

5.2.2 Occurrence of Significant Cardiovascular AEs and SAEs

The following Cardiovascular adverse events will be examined individually: cardiovascular mortality, blood pressure effects, edema formation, rhythm disturbances, and heart failure.

5.2.2a Cardiovascular Mortality

1. The crude rates of death due to cardiovascular disease in both the celecoxib and in the active control groups were higher than in the placebo group. For each of these analyses, the mortality rate for the active control group was numerically greater than the celecoxib group.

Mortality in deaths per patients exposed

Table 5.1.1.2.3 Calculation of crude cardiovascular mortality incidence in deaths per patients exposed in NDA 20-998^a.

Controlled N.A. OA/RA Trials	# of Deaths	# of Exposed Subjects	Mortality Incidence
Cardiac deaths during trial			
Placebo	0	1864	0.00%
Celecoxib	1	6376 ^c	0.02%
Active Control	2	2768	0.07%
All known cardiac deaths^b			
Placebo	0	1864	0.00%
Celecoxib	2	6376 ^c	0.03%
Active Control	2	2768	0.07%

a. Data from Integrated Safety Summary, including Text Tables 65-68.

b. Includes one death in the active control group and two deaths in the celecoxib group after trial completion. These deaths occurred >28 days after last dose of study medication.

Mortality in deaths per patient-years of exposure

It is also fruitful to calculate mortality using the data on patient-years of exposure as the denominator. These calculations are in the table below.

Table 5.1.1.2.4 Calculation of cardiovascular mortality rate in deaths per patient-years of exposure in NDA 20-998^a.

Controlled N.A. OA/RA Trials	# of Deaths	Patient-years of Exposure ^e	Mortality Rate
Cardiac deaths during trial			
Placebo	0	208	0.00%
Celecoxib	1	1020	0.10%
Active Control	2	535	0.37%
All known cardiac deaths^b			
Placebo	0	208	0.00%
Celecoxib	2	1020	0.20%
Active Control	2	535	0.37%

a. Data from Integrated Safety Summary, including Text Tables 65-68.

b. Includes one death in the active control group and two deaths in the celecoxib group after trial completion. These deaths occurred >28 days after last dose of study medication.

Cardiovascular mortality derived from Kaplan-Meier Plot

Table 5.1.1.2.5 Kaplan-Meier estimates for cumulative incidence rates for all mortality in the North American OA/ RA trials^a.

Controlled Studies, 24 week	All-Cause Deaths (n, %)	Cardiovascular Deaths (n, %)
Deaths ≤28 days after last dose of study drug		
Placebo	0 (0%)	0 (0%)
Celecoxib	2 (0.38)	1 (0.02%)
Active Control	4 (0.26%)	2 (0.12%)
All deaths		
Placebo	0 (0%)	0 (0%)
Celecoxib	4 (0.45%)	2 (0.05%)
Active Control	4 (0.22%)	2 (0.10%)

a. Data from sponsor-derived plots.

2. In the long-term, open-label trial, the cumulative incidence of cardiovascular death was between 0.17% and 0.35%.

Mortality in deaths per patients exposed

Table 5.1.1.2.3 Calculation of crude cardiovascular mortality in deaths/pts exposed^a.

Long-term, Open-label Trial	# of Deaths	# of Exposed Subjects	Mortality Incidence
Cardiac deaths before cut-off date	9	5155	0.17%
Known deaths during celecoxib use	14 ^d	5155	0.27%
All known cardiac deaths^c	15	5155	0.29%

a. Data from Integrated Safety Summary, including Text Tables 65-68.

c. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date for the ongoing trial (11.21.97). Also includes three deaths that occurred >28 days after last reported use of celecoxib (see tables 5.1.1.1 to 5.1.1.4).

d. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date for the ongoing trial (11.21.97).

Mortality in deaths per patient-years of exposure

It is also fruitful to calculate mortality using the data on patient-years of exposure as the denominator.

Table 5.1.1.2.4 Calculation of cardiovascular mortality rate in deaths per pt-years of exposure^a.

Long-term, Open-label Trial	# of Deaths	Patient-years of Exposure^c	Mortality Rate
Cardiac deaths before cut-off date	9	2672	0.33%
Known deaths during celecoxib use	14 ^d	4274	0.33%
All known cardiac deaths^c	15	4274	0.35%

a. Data from Integrated Safety Summary, including Text Tables 65-68.

c. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date for the ongoing trial (11.21.97). Also includes three deaths that occurred >28 days after last reported use of celecoxib (see tables 5.1.1.1 to 5.1.1.4).

d. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date (11.21.97).

Cardiovascular mortality derived from Kaplan-Meier Plot

The next table comes from the long-term trials, using various cut-offs for inclusion.

Table 5.1.1.2.6 Kaplan-Meier estimates for cumulative incidence rates for cardiovascular mortality in the open-label, long-term trial^a.

Long-term Open-Label Study (52 wk)	All-Cause Deaths (n, %)	Cardiovascular Deaths (n, %)
Deaths ≤28 days after last dose of study drug		
As of 11.21.97	10 (0.43%)	9 (0.39%)
As of 5.1.98	15 (0.38%)	14 (0.35%)
All deaths		
As of 5.1.98	18 (0.41%)	14 (0.35%)

a. Data from sponsor-derived plots.

3. Arranged according to last dose of celecoxib received, there was an apparent relationship between dose of celecoxib and mortality rate.

Table 5.1.1.2.7 Calculation of cardiovascular mortality rates in deaths per patient-years of exposure, arranged according to highest dose of celecoxib received, from the long-term trial^{a,b}.

Celecoxib Dose	Number of Deaths	Patient-years of Exposure ^d	Crude Mortality Rate ^c
100 mg	0	519	0%
200 mg	4	1271	0.31%
300 mg	2	340	0.59%
400 mg	3	465	0.64%

a. Data from Integrated Safety Summary, including Text Tables 65-68.

b. Data shown for deaths that occurred prior to cut-off date 11.21.97.

c. Mortality (for both total and cardiovascular deaths) in deaths/pt-yr (x100).

d. Data from ISS, Appendix table 4.3.

4. In the long-term trial, the predominate (90%+) cause of death for patients taking celecoxib at any dose was cardiovascular (see tables 5.1.1.2 and 5.1.1.3). The majority of these deaths represented progression of previously known cardiac disease (see individual narrative summaries, appendix one).

5. Examining the Kaplan-Meier survival curves for both controlled and long-term trials, there was no apparent relationship between any given duration of exposure and increased mortality (see sponsors figure 3, 4 and 5).

6. The demographics of the subjects in the controlled trials were estimated from the ICD-9 codes. Overall, 35-40% of the subjects had hypertension, 15% had a history of significant cardiac disease (i.e., MI, angina pectoris), 7-8% were diabetic, 7-10% were hyperlipidemic, and 3-4% had significant renal disease. No information about smoking history is available.

From Table 3.1.3.5 Significant cardiac and renal past medical history in the celecoxib North American controlled trials^a.

	Placebo N=1864 ^b	Celecoxib 25-400 mg N=5704 ^c	Active Controls N=2098 ^d
Cardiovascular Disease			
Angina Pectoris	57 (3.1%)	194 (3.4%)	75 (3.6%)
Coronary Atherosclerosis	70 (3.8%)	201 (3.5%)	82 (3.9%)
Congestive Heart Failure	24 (1.3%)	63 (1.1%)	25 (1.2%)
Hypertension (not otherwise specified)	732 (39.3%)	2172 (38.1%)	749 (35.7%)
CABG	31 (1.7%)	118 (2.1%)	39 (1.8%)
Myocardial Infarction (not otherwise specified)	54 (2.9%)	167 (2.9%)	74 (3.5%)
Endocrine Disease			
Diabetes Type I (uncomplicated)	26 (1.4%)	89 (1.5%)	34 (1.6%)
Diabetes Type II (uncomplicated)	114 (6.1%)	408 (7.2%)	156 (7.4%)
Hypothyroid	234 (12.6%)	659 (11.6%)	241 (11.5%)
Hyperlipidemia	108 (5.8%)	376 (6.6%)	137 (6.5%)
Obesity	131 (7.0%)	389 (6.8%)	148 (7.1%)
Renal/ GU Disease			
Renal calculus	64 (3.4%)	206 (3.6%)	93 (4.4%)
Hematuria	29 (1.6%)	65 (1.1%)	17 (0.8%)
UTI	95 (5.1%)	231 (4.0%)	76 (3.6%)

a. Data from NDA Integrated Safety Summary, Appendix 8.2. The database used includes studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087. Collected ICD-9 codes were used to calculate incidence rates for each group.

Conclusion regarding cardiovascular mortality

There are aspects of the dataset above that could suggest an association between celecoxib (and active control) use and increased cardiovascular mortality:

- 1) the increased relative rate of cardiovascular death in the celecoxib and active control groups during the controlled trials (0% for placebo, 0.02% for celecoxib, 0.12% for active control, see table 5.1.1.2.5),
- 2) the apparent relationship between dose of celecoxib and rate of cardiovascular death in the long-term, open-label trial (table 5.1.1.2.7), and
- 3) the preponderance of deaths due to cardiovascular disease in the open-label trial (tables 5.1.1.1.1 through 5.1.1.1.4).

Based on the demographics of the enrolled population, this interpretation would imply some effect of the drugs to accelerate cardiovascular disease in a population already at risk for it. The problems with this interpretation can be summarized as follows:

1) The overall small number of deaths that occurred in the controlled database (table 5.1.1.2.4). The occurrence of only 8 deaths during the controlled phase of the trials severely limits interpretation of the calculated mortality rates from these trials. The occurrence of a single death in the placebo group would eliminate the apparent differences in the mortality rates between treatment groups.

2) We don't have good comparator data to know what the 'expected' rate of cardiovascular death is in the OA/RA population, and we lack a control group for the long-term trial. Extrapolation from other population at low risk for cardiovascular disease, such as the primary prevention trials using Aspirin or cholesterol-lowering agents, is difficult because of differences in the clinical characteristics of the patient populations studied (see table 3.1.3.5). The ongoing Women's Health study may give some data in this regard, but has not yet released the pertinent data.

3) The lack of information about the sub-populations within the long-term database. While the apparent relationship between dose of celecoxib and rate of cardiovascular death is provocative (Table 5.1.1.2.7), patients who received higher doses of celecoxib could also have more advanced osteoarthritis and rheumatoid disease, and may have had it for a longer duration. If this were true, they might also be more likely to have received steroids and other potent medications, more likely to be hypertensive, and more likely to have other clinical illness that confounds the analysis. While the large majority of the deaths were cardiovascular, this might be expected in a population selected to exclude those with significant other medical disease, as was done in this case. The deaths, where examined by this reviewer, were also largely a progression of previously known cardiovascular disease.

In conclusion, the available data are inadequate either to exclude or confirm a link between celecoxib administration and cardiovascular death.

5.2.2b Blood Pressure Effects

1. The blood pressure (BP) effects of the study drugs were measured both during the trials and BP readings, and in the form of AEs and SAEs (tables 5.1.5.1, 5.1.2.1, 5.1.2.1, 5.1.2.3, 5.1.3.1). The reasons for withdrawal from the open-label trial also included hypertension (table 5.1.6.2 5.1.6.3, and 5.1.6.7). Blood pressures were also measured during each clinic visit, and those data summarized as change from baseline (table 5.1.5.1).

2. With regard to changes in measured BPs, administration of celecoxib and active control were associated with a nominally significantly higher mean systolic BP at the end of the trial, compared with placebo. While all three groups had a decrease in their mean systolic BP, the greatest decrease occurred in the placebo group compared with celecoxib and active control. No effect of celecoxib or active control on diastolic BP was detected.

From Table 5.1.5.1 Mean changes in blood pressure in the 12-week, controlled North American Arthritis trials of celecoxib from NDA 20-998^{a,b}.

Vital Sign Measured (Change from baseline)	Placebo	Celecoxib 400 mg BID	Active Controls
Systolic BP	-2.1±0.5	-0.5±0.5*	-0.3±0.6*
Diastolic BP	-0.6±0.3	-0.5±0.3	-0.5±0.3

a. Data from NDA Integrated Safety Summary, table 30.1.2. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

3. There was a higher incidence of 'hypertension' as an AE in the celecoxib and active control groups, relative to placebo (table 5.1.3.1). The incidence of hypertension for the '100-200 mg' groups was statistically significant (p=0.02) relative to placebo. The incidence of hypertension for the 'all celecoxib' and 'g' group was of borderline statistical significance relative to placebo (p=0.02).

Table 5.1.3.1 Adverse events in the North American Arthritis trials of celecoxib from NDA 20-998^a Part one: Cardiovascular AEs.

Hypotension and hypertension as AEs	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=4146	Active Controls N=2098
Hypertension ^c	12 (0.6%)	64 (1.1%)	55 (1.6%)	20 (1.0%)
Hypotension	1 (<0.1%)	1 (<0.1%)	0 (0%)	4 (0.2%)
Hypotension, Postural	0 (0%)	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)

a. Data from NDA Integrated Safety Summary, table 6.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

c. Includes both undifferentiated hypertension and aggravated hypertension.

4. The incidence of 'hypertension' as an SAE occurred in three celecoxib patients, compared with no placebo or active control patients in the controlled trials (table 5.1.2.1, 5.1.2.3).

5. Hypertension as a cause of withdrawal, occurred in 6 celecoxib patients in the controlled trials (0.1%), compared with 1 active control (<0.1%) and 0 placebo (0%), (table 5.1.6.7). There were 4 discontinuations (0.1%) in the long-term open-label trial for hypertension.

Table 5.1.6.7 Patients in the controlled OA/RA trials withdrawn due to hypertension^a.

Treatment Group/ Patient #	Preferred Term for AE
Placebo (n=1864)	
None	
Celecoxib 50-400 mg (n=5704)	
020-0123	Hypertension
020-0294	Hypertension
020-1147	Hypertension, Aggravated
054-0153	Hypertension
054-1396	Hypertension, Aggravated
071-2008	Hypertension, Aggravated
Active Control (n=2098)	
071-1737	Hypertension

a. Data from sponsor at reviewer's request.

Table 5.1.6.7 Patients in the long-term OA/RA trial (024) withdrawn due to hypertension^a.

Celecoxib Dose ^b / Patient #	Final Dose	Adverse Event	Days on Drug
Celecoxib 100 mg 054-0153	100	Hypertension	N/A, ongoing
Celecoxib 200 mg 020-0123 054-0629	200 200	Hypertension Hypertension	4, ongoing at day 465 42, ongoing at day 88
Celecoxib 400 mg 023-0051	400	Hypertension, Aggravated	374, ongoing

a. Data from sponsor at reviewer's request submitted 11.3.98.

Conclusions regarding blood pressure

The available data are sufficient to conclude that there is a probable association between celecoxib administration and the worsening of blood pressure. This worsening is primarily seen within 12 weeks of starting the treatment, but was of sufficient severity to lead to subject withdrawal from the study drug in both the short-term controlled and in the long-term studies. The association between the active control group and hypertension is less clear, as less data is available regarding long-term exposure. The use of NSAIDs has been linked to hypertension in other clinical databases.

5.2.2c Edema Formation

1. The incidence of edema was measured in the form of AEs and SAEs (tables 5.1.2.1, 5.1.3.1, 5.2.3.2,). The reasons for withdrawal from the open-label trial also included edema (table 5.1.6.2 5.1.6.3, and 5.1.6.7).

2. The incidence AEs for peripheral edema, and the combination of all recorded 'edema' categories, were nominally significantly higher in both celecoxib groups and the active control group, relative to placebo.

From Table 5.1.3.1 Edema as an adverse events identified in the N.A. arthritis trials from NDA 20-998^a.

Edema as an AE	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=4146	Active Controls N=2098
Edema, Generalized	0 (0%)	8 (0.14%)	5 (0.1%)	10 (0.5%)
Edema, Facial	8 (0.4%)	23 (0.4%)	17 (0.4%)	5 (0.2%)
Edema, Peripheral	21 (1.1%)	124 (2.2%)	89 (2.1%)	45 (2.1%)
Edema, Peri-orbital	0 (0%)	2 (<0.1%)	2 (<0.1%)	0 (0%)
Edema, Legs	0 (0%)	1 (<0.1%)	1 (<0.1%)	0 (0%)
Edema, All Categories	29 (1.6%)	158 (2.8%)	114 (2.7%)	60 (2.8%)

a. Data from NDA Integrated Safety Summary, table 6.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

3. There were no recorded SAEs for edema, including 'peripheral edema', 'generalized edema', or 'edema, legs' (table 5.1.3.1).

4. The incidence of edema causing subject discontinuation was low in the North American OA/RA controlled trials, and equal among the three treatment groups. Overall, 1 placebo, 4 celecoxib and 3 active control subjects withdrew for edema of any kind.

From Table 5.1.6.7 Patients in the controlled OA/RA trials withdrawn due to edema^a.

Treatment Group/ Patient #	Preferred Term for AE
Placebo (N=1864)	
021-0445	Edema, Peripheral
Celecoxib 50-400 mg (N=5704)	
054-0758	Peripheral Edema
060-0447	Peripheral Edema
087-0243	Peripheral Edema
012-0483	Generalized Edema
Active Control (N=2098)	
023-0671	Generalized Edema
023-0827	Generalized Edema
071-1310	Peripheral Edema

a. Data from sponsor at reviewer's request.

In the long-term trial there were 10 discontinuations for edema (0.2%). Note the occurrence of facial edema in the long-term trial severe enough to warrant discontinuation.

Table 5.1.6.7 Patients on celecoxib in the long-term OA/RA trial withdrawn due to renal adverse events^a.

Celecoxib Dose ^b / Patient #	Adverse Event
Celecoxib 100 mg	
020-0213	Edema, ankle and peripheral
020-0313	Edema, peripheral and lower extremity
054-0589	Edema, peripheral
013-0285	Edema, generalized
Celecoxib 200 mg	
021-0946	Edema, peripheral and lower extremity
021-0883	Edema, peripheral and lower extremity
022-0114	Edema, facial
054-0595	Edema, peripheral and lower extremity
Celecoxib 300 mg	
023-1173	Edema, facial
023-0671	'Urine abnormal' & 'Urine smells'
	Edema, generalized

a. Data from sponsor at reviewer's request submitted 11.3.98.

b. Dose is last recorded does taken by the patient at time of AE.

5. There was no statistically significant association between ≥ 1 kg weight gain and the occurrence of 'peripheral edema' in a subset of all patients with edema as an AE, although a higher % of both celecoxib and active control group patients had both.

From Table 5.1.4.2.3 Occurrence of edema and weight gain in the North American Arthritis trials^a.

Syndrome	Placebo N=1864	Celecoxib N=3512	Active Control N=1099
AEs			
Edema, Generalized ^a	0 (0%)	5 (0.1%)	10 (0.5%)
Edema, Peripheral	21 (1.1%)	89 (2.1%)	45 (2.1%)
Edema, Generalized^b	0 (0%)	6 (0.2%)	9 (0.8%)
Edema, Peripheral	13 (1.1%)	83 (2.5%)	24 (2.2%)
Weight Gain ≥ 1 kg	201 (17.7%)	879 (26.0%)	304 (27.7%)
Both Edema and Weight Gain^b	6 (0.5%)	24 (0.7%)	9 (0.8%)

a. Data from corrected tables from the ISS, table 3.1.3.6, dated 9.16.98 including only 100 and 200 mg dose groups.

b. Data from sponsor, only for those patients with both weight and edema AE data. Includes 50 to 400 mg doses.

However, the changes in weight for the trials were quite variable depending on the patient population examined. Overall, males and females that were heavier at baseline tended to gain more weight in the celecoxib and active control groups, relative to placebo. This spread may have obscured an association between weight gain and edema (edema being easier to detect in lighter individuals).

From Table 5.1.5.1 Mean changes in weights in the 12-week, controlled North American Arthritis trials of celecoxib from NDA 20-998^{a,b}.

Vital Sign Measured (Change from baseline)	Placebo	Celecoxib 400 mg BID	Active Controls
Male Weight (Baseline ≤85 kg)	+1.43±0.9	+0.41±0.2*	0.97±0.2*
Male Weight (Baseline >85 kg)	-0.5±0.3	+1.37±0.4*	+0.56±0.2*
Female Weight (Baseline ≤70 kg)	+0.89±0.6	+0.22±0.1	+0.41±0.1
Female Weight (Baseline >70 kg)	-0.23±0.1	+0.12±0.1*	+0.24±0.1*

a. Data from NDA Integrated Safety Summary, table 30.1.2. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

b. * represent nominal significance versus placebo.

Conclusion regarding edema

The available data are sufficient to conclude that there is a probable association between either celecoxib or active control administration and the development of clinically significant edema, especially peripheral edema. This edema is of sufficient severity to lead to subject withdrawal from study drug in both the controlled and in the long-term trials. The lack of a statistical association between edema and weight gain may be attributable to variability in weights both from visit to visit as well as differences in edema detection in different groups of patients.

5.2.2d Rhythm disturbances

1. Changes in mean heart rate were monitored in the controlled trials. Celecoxib administration was associated with a small, but nominally significant, slowing of the heart rate relative to control.

From Table 5.1.5.1 Mean changes in pulse rate in the controlled North American arthritis trials^{a,b}.

	Placebo	Celecoxib 400 mg BID	Active Controls
Pulse Rate	0.8±0.3	-0.4±0.3*	0.3±0.4

a. Data from NDA Integrated Safety Summary, table 30.1.2.

b. * indicates nominally significant difference with placebo.

2. The reported rate of AEs related to rhythm disturbances were also higher in the celecoxib and active control groups, including tachycardias, palpitations, and 'arrhythmia.'

From Table 5.1.3.1 Arrhythmias identified as adverse events in the controlled trials of celecoxib^a.

Clinical AE	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=4146	Active Controls N=2098
Cardiovascular System				
Arrhythmia ^d	2 (0.1%)	7 (0.1%)	6 (0.1%)	6 (0.3%)
Atrial fibrillation	1 (<0.1%)	1 (<0.1%)	0 (0%)	1 (<0.1%)
Bradycardia	0 (0%)	0 (0%)	0 (0%)	4 (0.2%)
Tachycardia ^e	1 (<0.1%)	16 (0.3%)	9 (0.2%)	2 (0.1%)
Palpitations	1 (<0.1%)	22 (0.4%)	13 (0.3%)	11 (0.5%)
Ventricular arrhythmia	0 (0%)	0 (0%)	0 (0%)	1 (<0.1%)

a. Data from NDA Integrated Safety Summary, table 6.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

d. Includes undifferentiated arrhythmia, atrial and ventricular arrhythmia.

e. Includes undifferentiated and supraventricular tachycardia.

3. The rate of rhythm disturbances as SAEs was higher in the celecoxib and active control groups when compared with placebo. These rhythm disturbances were scattered among arrhythmias with separate pathophysiologies, including palpitations, atrial fibrillation, and supraventricular tachycardia.

From Table 5.1.2.1 Arrhythmias identified as SAEs in the U.S. Arthritis trial database^a.

Cardiovascular System SAE	Placebo N=1864	Celecoxib 25-400 mg N=5083	Active Controls N=2098
Rhythm Disturbances ^b	1 (<0.1%)	5 (0.1%)	2 (0.1%)

a. Data from NDA Integrated Safety Summary, Appendix Table 22.1, and electronic datasets.

b. Includes the following terms: arrhythmia; atrial arrhythmia; atrial fibrillation; heart block; palpitation; & supraventricular tachycardia.

The next table shows the incidence of relevant serious adverse events that occurred in the long-term, open-label celecoxib trials. Overall, there were few reported arrhythmic SAEs.

Table 5.1.2.2 Arrhythmias as SAEs collected in long-term, open-label database^a.

Cardiovascular System SAE	Combined N=4499
Cardiac Arrest	1 (<0.1%)
Bradycardia	2 (<0.1%)
Atrial Fibrillation	4 (<0.1%)
Ventricular Fibrillation	1 (<0.1%)

a. Data from NDA Integrated Safety Summary, Table 22.2, and electronic datasets. Numbers shown as individual subjects.

Note that in some cases, a subject may have had more than one serious adverse event in the same category, which is not captured here.

b. Includes coronary thrombosis and myocardial infarction.

4. More patients in the celecoxib group (9, 0.16%), and active control group (3, 0.14%) were withdrawn due to 'Arrhythmia' as an SAEs than in the placebo group (1, <0.1%). These withdrawals were also scattered among arrhythmias with separate pathophysiologies, including palpitations, atrial fibrillation, and supraventricular tachycardia.

From Table 5.1.6.3 Arrhythmic adverse events leading to subject discontinuation in the controlled OA/RA trials^a.

	Placebo N=1864	Celecoxib 50-400 mg BID N=5704	Active Control N=2098
Arrhythmia ^c	1 (<0.1%)	9 (0.16%)	3 (0.14%)

a. Data from Integrated Safety Summary, Appendix table 6.4..

c. Includes 'arrhythmia', atrial arrhythmia, atrial fibrillation, palpitation, tachycardia, and supraventricular tachycardia.

There were no discontinuations for non-fatal rhythm disturbances in the long-term trials. One individual had ventricular fibrillation during a large MI.

5. The sponsor examined the time-dependence of cardiovascular events leading to withdrawal, including rhythm disturbances (table 5.1.6.4). For atrial fibrillation, palpitations, and ventricular tachycardia, there was no pattern of increased occurrence with increased exposure.

Conclusion regarding arrhythmias

There was a numerical excess of arrhythmias of several types in both the celecoxib and active control groups relative to placebo. In particular, supraventricular arrhythmias are more common in the celecoxib group. These arrhythmias, however, do not share a common pathophysiology, and there is no attractive mechanism for a direct effect of a COX-2 inhibitor on the entire cardiac conduction system. There is also no precedent for this adverse event from other NSAIDs, or from the pre-clinical toxicology data available. One possibility (unproven) is that this phenomenon, if real, reflects subtle effects of NSAIDs on electrolytes in susceptible patients.

In conclusion, insufficient data exist to determine the clinical significance of this finding, or whether this observation is linked to the numerical increase in cardiac deaths in the two groups relative to control.

5.2.2e Heart failure

1. Cardiac failure was rarely reported as an AE in the controlled trial database.

From Table 5.1.3.1 Heart failure as an AE in the controlled trials^a

Cardiac Failure as an AE	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=4146	Active Controls N=2098
Cardiac Failure ^b	1 (<0.1%)	5 (0.1%)	4 (0.1%)	2 (0.1%)

a. Data from NDA Integrated Safety Summary, table 6.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

b. Includes left, right, and undifferentiated cardiac failure.

2. Heart failure, as a SAE, occurred in two celecoxib patients, one placebo patient, and no active control patient. Withdrawal due to heart failure occurred in one placebo patient (<0.1%), 5 celecoxib patients (0.1%) and no active control patients (0%).

Conclusion regarding heart failure

There is inadequate data to assess the administration of celecoxib to the occurrence of heart failure. With the available data, there is no evidence of an adverse effect of celecoxib on CHF.

5.2.2f Myocardial infarction and Angina Pectoris

1. The AEs, 'MI' and 'Coronary Artery Disorder' occurred in small numbers of patients in all three treatment groups.

From Table 5.1.3.1 Cardiac AEs in the North American Arthritis trials of celecoxib from NDA 20-998^a

Myocardial, Pericardial and Valve Disorders as AE	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=4146	Active Controls N=2098
Angina Pectoris ^f	5 (0.3%)	18 (0.3%)	14 (0.3%)	6 (0.3%)
Coronary Artery Disorder	2 (0.1%)	6 (0.1%)	5 (0.1%)	0 (0%)
Myocardial Infarction (MI) ^g	2 (0.1%)	10 (0.2%)	9 (0.2%)	2 (0.1%)
MI + Coronary Artery Disorder	4 (0.2%)	16 (0.3%)	14 (0.3%)	2 (0.1%)

a. Data from NDA Integrated Safety Summary, table 6.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

c. Includes both undifferentiated hypertension and aggravated hypertension.

f. Includes 'aggravated' and 'unstable' angina pectoris.

g. Includes 'Thrombosis, coronary'.

2. MI and Angina occurred equally as SAEs, and as AEs leading to withdrawal, in the three treatment groups (table 5.1.2.1 and 5.1.6.4).

From Table 5.1.6.3 Cardiovascular adverse events leading to subject discontinuation in the controlled North American OA/RA trials^a.

Cardiac AE leading to discontinuation	Placebo N=1864	Celecoxib 50-400 mg BID N=5704	Active Control N=2098
Angina ^d	2 (0.1%)	2 (<0.1%)	1 (<0.1%)
Myocardial infarction	2 (0.1%)	6 (0.1%)	2 (0.1%)

a. Data from Integrated Safety Summary, Appendix table 6.4.

d. Includes angina pectoris, aggravated angina pectoris and unstable angina.

In the long-term open-label trial, there were 8 individuals withdrawn due to myocardial infarction.

Conclusion regarding myocardial ischemic adverse events

There was no clear evidence that linked the occurrence of any specific cardiac SAE and/or AE, including those leading to withdrawal, with the administration of celecoxib. The database is inadequate to completely exclude an effect on these AEs, however.

5.2.3 Renal Adverse Events

The following categories of renal adverse events will be examined: clinically significant renal adverse events, and changes in renal laboratories. The renal laboratories section will be broken into the following subsections: changes in BUN, changes in creatinine, proteinuria and other urinary abnormalities, and changes in serum electrolytes (potassium, sodium, calcium, chloride and phosphate).

5.2.3a Clinical Renal Adverse Events

The incidence of acute renal failure was measured in the form of AEs and SAEs both during the controlled and the long-term trials (tables 5.1.2.1, 5.1.3.1, 5.2.3.2,). The reasons for withdrawal from the open-label trial also included 'uremia,' and 'elevated creatinine' (table 5.1.6.2 5.1.6.3, and 5.1.6.7).

1. Two individuals taking celecoxib had acute renal failure requiring dialysis in the controlled trials (versus none in the active control or placebo groups). One was due to repeated quinine use, the other associated with obstructive uropathy.

1. Patient 047-0030 was a 70-year-old female with a prior history of labile vascular hypertension, and urinary system disorders including urethral stenosis, urgency, and bladder spasms. Concomitant medications were: captopril, chlorpheniramine, docusate sodium, aspirin, estrogen, etidronate, fluconazole, dexamethasone, oxybutynin, pravastatin, quinine sulfate, and verapamil. Three weeks after starting celecoxib 400 mg BID, she experienced leg cramps for which she took quinine and subsequently experienced headache and pruritus. One week later, she repeated a single dose of quinine and again experienced headache and pruritus, but also nausea, vomiting, diarrhea, chills, and confusion. Four days later she was hospitalized with a fever and a creatinine level of 9.1 µmol/L. She was diagnosed with hemolytic uremic syndrome presumed due to quinine sulfate. Treatment included plasmapheresis, hemodialysis, and platelet transfusion.

2. Patient 024-1490002 was a 65- year-old male with a medical history of hypertension, depression, nocturia and RA. Concurrent medications included gold sodium thiomalate, terazosin, fosinopril, metoprolol, prednisone, and combination perphenazine and amitriptyline. The patient took celecoxib 100 mg BID for 12 weeks in a double-blind clinical RA trial. After successfully completing the trial, he was admitted to the long-term open-label trial. He was instructed to take celecoxib 200 mg BID, but for unknown reasons, he took only 100 mg BID. The patient returned at week 2 and no abnormalities were noted. Four days after he was seen for his "Week 6" visit, his urine output decreased and he felt ill. This was approximately one week following an endoscopic procedure associated with anesthesia. (Laboratory results from the Week 6 Visit revealed his serum creatinine to be 8.6 mg/dL and his BUN to be 61 mg/dL, significantly higher than his Baseline values, which were 1.4 mg/dL and 21 mg/dL, respectively). Five days later, study medication was stopped when he was hospitalized with a serum creatinine level of 19.4 mg/dL and a BUN of 116 mg/dL. During his hospitalization, he required hemodialysis on two occasions. Ultrasound examination showed bilateral hydronephrosis. He was scheduled for cystoscopy and retrograde ureteroscopy and possible stent placement when he developed significant large volume diuresis with normalization of his renal function. He recovered and was discharged from the hospital five days later. One week later, his serum creatinine value was 1.8 mg/dL and his BUN was 33 mg/dL.

2. In the long-term trial, 148 (3.3%) of the patients had the combination of proteinuria and elevated BUN/Crt. Of these, 27 (0.6%) ended the trial with proteinuria and an elevated BUN or Crt at last visit.

Seven individuals without proteinuria at the start of the trial ended with 2+ proteinuria or greater. In addition, three had markedly abnormal BUN/ creatinine values at the last testing (one of these is summarized above, patient 14-90002). Follow-up information for these individuals is not available.

5.1.4.2.13 Patients with marked abnormalities in final BUN/Crt from proteinuria/BUN/Crt cluster^a.

Patient #	Days on Celecoxib	Baseline/ Final Crt (µmol/l and mg/dl)	Baseline/ Final BUN (mmol/l)
014-0002	484	168/ 239 (1.9/ 2.7)	14.3/ 26.1 (43/ 80)
013-70004	183	53/ 168 (0.6/ 1.9)	7.9/ 15.4 ^b (24/ 46)
014-90002	122	124/ 760 (1.4/ 8.6)	10.7/ 21.8 (32/ 65)

a. Data from examination of individual line-listings from SAS datasets provided by sponsor.
b. BUN 23.9. Crt 194 on labs drawn 16 days earlier.

3. There were several other patients who experienced renal SAEs requiring discontinuation from the controlled and open-label trials. These are summarized below. Note in the open-label withdrawals that for many of the patients the adverse event was ongoing at time of last information. Using the patients listed below, the relative rates of withdrawal for 'renal adverse events' were 0.21%, 0.27%, and 0.24% for the placebo, celecoxib and active control groups, respectively. No cases of nephrotic syndrome or papillary necrosis were detected in the NDA database.

From Table 5.1.6.7 Patients in the controlled OA/RA trials withdrawn due to renal adverse events^a.

Treatment Group/ Patient #	Preferred Term for AE
<u>Placebo (n=1864)</u>	
020-880	Hematuria
021-0445	Edema, Peripheral
022-0345	Renal Calculus
060-0441	Renal Function, Abnormal
<u>Celecoxib 50-400 mg (n=5704)</u>	
054-0501	Creatinine Increased
020-0123	Hypertension
054-0758	Peripheral Edema
060-0447	Peripheral Edema
087-0243	Peripheral Edema
020-0294	Hypertension
020-1147	Hypertension, Aggravated
021-1340	Creatinine Increased
054-0153	Hypertension
054-1396	Hypertension, Aggravated
071-2008	Hypertension, Aggravated
071-3061	Renal Calculus
012-0483	Generalized Edema
047-0030	Uremia
047-0320	Hyperkalemia
<u>Active Control (n=2098)</u>	
023-0671	Generalized Edema
023-0827	Generalized Edema
071-1250	Creatinine Increased
071-1310	Peripheral Edema
071-1737	Hypertension

a. Data from sponsor at reviewer's request.

Withdrawals due to renal adverse events in the long-term, open-label trial were also collected by the sponsor, and are listed below.

Table 5.1.6.7 Patients in the long-term OA/RA trial (024) withdrawn due to renal adverse events^a.

Celecoxib Dose ^b / Patient #	Final Dose	Adverse Event	Days on Celecoxib
Celecoxib 100 mg			
054-0153	100	Hypertension	N/A
021-0033	100	Increased BUN	16, ongoing
021-1043	100	Increased BUN Increased Creatinine Hyperkalemia	133, ongoing at day 138
020-0213	100	Edema, ankle and peripheral	93
020-0313	100	Edema, peripheral and lower extremity	285, ongoing
054-0854	100	Renal insufficiency Increased Creatinine	76, ongoing
054-0589	100	Edema, peripheral	51, lasted 6 days
013-0285	100	Edema, generalized	4, ongoing
Celecoxib 200 mg			
020-0123	200	Hypertension	4, ongoing at day 465
022-0975	200	Acute Renal Failure	127, ongoing
021-0946	200	Edema, peripheral and lower extremity	34, ongoing at day 37
021-0883	200	Edema, peripheral and lower extremity	32
022-0114	200	Edema, facial	3
020-1071	200	Proteinuria, Albuminuria	5, ongoing at day 118
023-0393	200	Hematuria	177, ongoing
054-0595	200	Edema, peripheral and lower extremity	85, ongoing
054-0629	200	Hypertension	42, ongoing
Celecoxib 300 mg			
023-1173	300	Edema, facial	N/A
023-0671	300	'Urine abnormal' & 'Urine smells' Edema, generalized	N/A, ongoing at day 310
Celecoxib 400 mg			
012-0090	400	Azotemia & Increased Creatinine	455, lasted 34 days
022-0313	400	Increased Creatinine	167, lasted 17 days
023-0051	400	Hypertension, Aggravated	374, ongoing

a. Data from sponsor at reviewer's request submitted 11.3.98.

Time constraints have precluded the review of the individual case report forms for these individuals.

Conclusion regarding clinical renal adverse events

The NDA does not reveal a strong signal pointing towards substantial clinically serious renal disease (i.e., large number of patients with acute renal failure requiring dialysis, nephrotic syndrome, papillary necrosis) associated with celecoxib administration. There are individuals with substantial clinical AEs who received celecoxib. In particular, the increased % of subjects withdrawn due to worsened hypertension and edema in both the short- and long-term trials suggest, in combination with the observed effects of celecoxib on these parameters otherwise (see below), that celecoxib is not placebo with regard to its potential clinically-relevant renal effects. These events also support the conclusion that celecoxib resembles NSAIDs with regard to the renal adverse effects. No unique renal toxicity due to celecoxib was identified. In addition, no renal toxicity normally seen with NSAIDs was identified that occurred at a higher rate in celecoxib. A larger database would be necessary to determine the incidence of rarer, more serious renal AEs such as papillary necrosis, nephrotic syndrome or interstitial nephritis.

5.2.3b Changes in Renal Laboratories

Changes in BUN

1. There was a small, but significant increase in the BUN, as measured from baseline to the final measured value in the controlled trials in the celecoxib group. This was significantly different from the placebo, where there was a small decrease in BUN over the same period (see table 5.1.4.1.3).

From Table 5.1.4.1.3 Changes in final measured BUN in the controlled N.A. arthritis trials^a.

Changes in Final Visit Lab Values from Baseline	Celecoxib 400 mg	Placebo	Active Controls	p Value Celecoxib vs. Placebo	p Value Celecoxib vs. Active Cntrl	p Value Active Cntrl vs. Placebo
BUN (mmol/l)	0.27±0.063	-0.57±0.061	0.55±0.071	<0.001	0.003	<0.001

a. Data from NDA Integrated Safety Summary, table 25.1.2. The database used is from studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087. Number of subjects in each measurement varies between 410 and 440 (see table 25.1.2 for details).

2. Significantly more patients in the celecoxib and active control groups developed high BUNs after starting with normal BUN in the controlled trials (see table 5.1.4.1.5).

From Table 5.1.4.1.5 Shift in serum BUNs in the 12-week, controlled N.A. arthritis trials^a.

Maximal Change in Lab Value	Placebo	Celecoxib 400 mg	Active Controls
BUN (mmol/l)			
High (9.3-14.3 mmol/l)	5/420 from Normal 3/11 from High	17/409 from Normal 8/10 from High	21/423 from Normal 6/11 from High
Extreme high	None	None	0/1 from Extreme High

a. Data from NDA Integrated Safety Summary, table 5.1.2. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

3. Put another way, significantly more patients in the celecoxib and active control groups developed an elevated BUN (>6.7 mmol/l = 20 mg/dl) during the controlled trial.

From Table 5.1.4.2.5 Elevated BUNs in the controlled NA trials^a.

Lab Abnormality	Placebo N=1136	Celecoxib N=2256	Active Control N=1099
BUN >6.7 mmol/l	140 (12.3%)	675 (29.9%)	482 (43.9%)

a. Data from analyses performed by sponsor, and not independently confirmed by FDA.

4. There was also an increased incidence of extreme elevations in BUN in the controlled trials, relative to placebo (>14.3 mmol/l = 40 mg/dl) (see table 5.1.4.2.3). The overall number of such patients, however, is small.

From Table 5.1.4.2.3 Incidence of elevated BUN in the North American 12-week Arthritis trials.

AE/ Lab Value	Placebo N=1136	Celecoxib 100 mg N=1131	Celecoxib 200 mg N=1125	Celecoxib 400 mg N=434	Active Control N=1099
Serum Labs					
BUN >6.7 mmol/l ^b	140 (12.3%)	296 (26.2%)	379 (33.7%)	147 (33.9%)	482 (43.9%)
BUN >14.3 mmol/l ^c	0 (0%)	1 (<0.1%)	4 (0.4%)	0 (0%)	2 (0.2%)

a. Data from data submitted to FDA 10.9.98 from sponsor, and not independently confirmed by FDA reviewer.

b. 20 mg/dl.

c. 40 mg/dl.

5. The incidence of AEs for renal failure depended on the specific measure. In the controlled database, there was a small increase in the incidence of 'increased BUN' in the celecoxib group relative to control. 'Nephritis' occurred in one celecoxib patient and two active control patients (no placebo patients). 'Uremia' occurred in one celecoxib patient, and in no other patients.

From Table 5.1.3.1 Adverse renal events in the controlled trials from NDA 20-998^a

Renal System AE	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=3512	Active Controls N=2098
Uremia	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)
BUN Increased	1 (<0.1%)	11 (0.2%)	7 (0.2%)	2 (0.1%)
Nephritis	0 (0%)	1 (<0.1%)	1 (<0.1%)	2 (0.1%)

a. Data from NDA Integrated Safety Summary, table 6.2 and 31.3.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

6. In the long-term database, the incidence of increased BUN identified as an Adverse Event was 0.3% (see table 5.1.3.2). The incidence of abnormally elevated BUN (>6.7 mmol/l = 20 mg/dl) was 44.3% in the long-term open-label trial.

Table 5.1.4.2.4 Incidence of selected adverse events and laboratory abnormalities in the North American 12-week Arthritis trials.

Serum Labs	Celecoxib N=4499
BUN >6.7 mmol/l ^b	1995 (44.3%)
BUN >14.3 mmol/l ^c	14 (0.3%)
Creatinine >132 µmol/l ^d	53 (1.2%)
Creatinine >159 µmol/l ^e	10 (0.2%)

a. Data from data submitted to FDA 10.9.98 from sponsor.

b. 20 mg/dl.

c. 40 mg/dl.

d. 1.5 mg/dl.

e. 1.8 mg/dl

f. 3.0 mg/dl.

7. Two patients in the celecoxib groups were discontinued for elevated in BUN in the long-term trial, both within 180 days of starting celecoxib. Other renal discontinuations are also shown in the table.

From Table 5.1.6.7 Patients in the long-term trial (024) withdrawn for increased BUN or acute renal failure^a.

Celecoxib Dose ^b / Patient #	Final Dose	Adverse Event
Celecoxib 100 mg		
021-0033	100	Increased BUN
021-1043	100	Increased BUN
		Increased Creatinine
		Hyperkalemia
054-0854	100	Renal insufficiency
		Increased Creatinine
Celecoxib 200 mg		
022-0975	200	Acute Renal Failure
Celecoxib 400 mg		
012-0090	400	Azotemia
		Increased Creatinine
022-0313	400	Increased Creatinine

a. Data from sponsor at reviewer's request submitted 11.3.98 .

Conclusions regarding BUN

These will be intergrated into the conclusions regarding elevations in creatinine below.

Changes in Creatinine

1. Regardless of how it was measured, all three treatment groups had similar incidence of elevated mean serum creatinine (see table 5.1.4.1.5 and 5.1.4.2.3). This was true for both mild (>132 mmol/l = 1.5mg/dl) or marked elevation (>159 mmol/l = 1.8 mg/dl). There was a numerical and % excess of patients in the celecoxib group who had elevated creatinine at some time during the controlled trials, but the trend was not statistically significant.

Table 5.1.4.2.3 Incidence of elevated serum creatinines in the North American 12-week Arthritis trials.

Elevations in creatinine	Placebo N=1136	Celecoxib 100 mg N=1131	Celecoxib 200 mg N=1125	Celecoxib 400 mg N=434	Active Control N=1099
Serum Labs					
Creatinine >132 µmol/l^d	6 (0.5%)	7 (0.6%)	15 (1.3%)	2 (0.5%)	14 (1.3%)
Creatinine >159 µmol/l^e	0 (0%)	1 (<0.1%)	3 (0.3%)	0 (0%)	0 (0%)

a. Data from data submitted to FDA 10.9.98 from sponsor, and not independently confirmed by FDA reviewer.

d. 1.5 mg/dl.

e. 1.8 mg/dl

2. No SAEs or AEs related to increased creatinine were reported by the investigators (tables 5.1.2.3 and 5.1.3.1) in the short-term trials.

3. Regarding patients withdrawn from the controlled trials for lab abnormalities, no placebo patients, two celecoxib patients, and one active control patient withdrew for elevated creatinine (table 5.1.6.7). One patient in the placebo group was withdrawn for 'abnormal renal function.'

Table 5.1.6.7 Patients in the controlled OA/RA trials withdrawn due to renal adverse events^a.

Treatment Group/ Patient #	Preferred Term for AE
Placebo	
060-0441	Renal Function, Abnormal
Celecoxib 50-400 mg	
054-0501	Creatinine Increased
021-1340	Creatinine Increased
Active Control	
071-1250	Creatinine Increased

a. Data from sponsor at reviewer's request.

4. Regarding patients withdrawn from the long-term trial, there were none withdrawn for elevated creatinine (table 5.1.6.6). One was discontinued for 'acute renal failure.' These patients are listed as part of the discussion regarding elevated BUN above.

Conclusions regarding elevated BUN and Creatinine

A reasonable summary of the data presented above is the following: while there is no clear increase in clinically significant renal disease (i.e. renal failure requiring dialysis, interstitial nephritis, nephrotic syndrome), there is an increase in the number of patients who developed elevations of BUN relative to placebo. There was also a trend towards an increased incidence of elevated serum creatinine values in both the celecoxib and active control groups relative to placebo. In addition, there is a group of individuals withdrawn from the long-term trial for acute renal deterioration (marked by increased BUN, creatinine, 'azotemia', etc.). While none of these can absolutely be ascribed to celecoxib use at present, the pattern suggests that celecoxib may indeed have clinically relevant renal toxicity. The pattern of withdrawals and SAEs is also similar to what might be expected for an NSAID, with known adverse effects on the kidney. The absence of examples of reported severe renal injury (i.e., nephrotic syndrome, papillary necrosis) can be expected, based on the number of patients exposed in the database and the reported incidence of these events following the use of other NSAIDs.

In conclusion, there is a probable association between celecoxib use and significant changes in renal function, as marked by increases in lab measurements and withdrawals from the clinical trials. As stated above, the database is too small to evaluate the effects of celecoxib on rare, severe, renal injury, including nephrotic syndrome and papillary necrosis.

5.2.3c Proteinuria and other Urinary Abnormalities

1. Urinary abnormalities were measured during the clinic visits and the summarized. The only significant difference in this analysis was in the incidence of glycosuria (increased in celecoxib). When diabetics were removed from this analysis, there was no significant difference between the three groups.

From Table 5.1.4.1.1 Incidence of extreme urinalysis values in the controlled North American Arthritis trials of celecoxib from NDA 20-998^a.

Urinary Abnormalities	Placebo N ≈ 1080 ^b	Celecoxib 400 mg N ≈ 3250 ^b	Active Controls N ≈ 1060 ^b
Urine Protein >1+	16 (1.6%)	44 (1.4%)	9 (0.9%)
Urine Glucose >1+	17 (1.7%)	88 (2.7%)	15 (1.5%)
Urine pH >8.5	0 (0%)	1 (<0.1%)	2 (0.2%)
Urine Ketones >1+	2 (0.2%)	5 (0.1%)	3 (0.3%)
Urine RBCs >10 per HPF	39 (3.9%)	142 (4.4%)	46 (4.5%)
Urine WBCs >20 per HPF	42 (4.2%)	130 (4.0%)	54 (5.3%)

a. Data from NDA Integrated Safety Summary, table 24.1. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

b. The number of available subjects varied slightly from test to test.

2. Urinary abnormalities were also examined as a shift from baseline. There was no trend towards a higher incidence of any abnormalities in the celecoxib group relative to control (see table 5.1.4.1.6 for details).

3. Urinary abnormalities that resulted in AEs included albuminuria, hematuria, and pyuria. 'Albuminuria' was reported as an AE in a higher % of the celecoxib group, relative to placebo. Hematuria and pyuria occurred in equal incidence for all three treatment groups. No SAEs related to urinary abnormalities were reported.

From Table 5.1.3.1 Urinary AEs in the North American Arthritis trials of celecoxib from NDA 20-998^a.

Urinary AEs	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=3512	Active Controls N=2098
Albuminuria	2 (0.1%)	15 (0.3%)	12 (0.3%)	1 (<0.1%)
Hematuria	3 (0.2%)	11 (0.2%)	7 (0.2%)	2 (0.1%)
Pyuria	2 (0.1%)	3 (<0.1%)	2 (<0.1%)	2 (0.1%)

a. Data from NDA Integrated Safety Summary, table 6.2 and 31.3.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

4. No SAEs related to proteinuria were recorded in the controlled trials. No cases of nephrotic syndrome were reported.

5. There was a significant association between the development of proteinuria and an increased BUN in the controlled trials.

Table 5.1.4.2.12. Association between proteinuria and elevated BUN/ Crt in controlled trials^a.

Abnormality	Placebo N=1136	Celecoxib N=2256	Active Control N=1099
Urine Protein >trace	43 (3.8%)	85 (3.8%)	48 (4.4%)
Creatinine >132 mmol/l	6 (0.5%)	22 (1.0%)	13 (1.3%)
Creatinine >159 mmol/l	0 (0%)	4 (0.2%)	0 (0%)
BUN >6.7 mmol/l	140 (12.3%)	675 (29.9%)	482 (43.9%)
BUN >14.3 mmol/l	0 (0%)	5 (0.2%)	2 (0.2%)
Proteinuria and either Crt >132 or BUN >6.7 mmol/l (at least 2)	6 (0.5%)	35 (1.6%)	23 (2.1%)
Proteinuria or Crt >132 and/or BUN >6.7 mmol/l (at least 1)	142 (12.5%)	680 (30.1%)	486 (44.2%)
Proteinuria and/or Crt >159 and/or BUN >13.4 mmol/l (at least 2)	0 (0%)	1 (<0.1%)	0 (0%)
At least two abnormalities present on last available labs	2 (0.2%)	14 (0.6%) ^b	5 (0.45%)

a. Data from analyses performed by sponsor, and not independently confirmed by FDA.

b. p Values 0.07 vs. placebo, using unadjusted chi square.

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This association extended to the long-term trial, where 148 (3.3%) of the patients had the combination of proteinuria and elevated BUN/ Cr. Of these, 27 (0.6%) ended the trial with proteinuria and an elevated BUN or Cr at last visit.

Seven individuals without proteinuria at the start of the open-label trial ended with 2+ proteinuria or greater. In addition, three had markedly abnormal BUN/ creatinine values at the last testing.

From Table 5.1.4.2.13 Patients with marked abnormalities in final BUN/Crt from proteinuria/BUN/Crt cluster^a.

Patient #	Days on Celecoxib	Baseline/ Final Cr (mmol/l and mg/dl)	Baseline/ Final BUN (mmol/l)
014-0002	484	168/ 239 (1.9/ 2.7)	14.3/ 26.1 (43/ 80)
013-70004	183	53/ 168 (0.6/ 1.9)	7.9/ 15.4 ^b (24/ 46)
14-90002	122	124/ 760 (1.4/ 8.6)	10.7/ 21.8 (32/ 65)

a. Data from examination of individual line-listings from SAS datasets provided by sponsor.

b. BUN 23.9, Cr 194 on labs drawn 16 days earlier.

6. One individual in the long-term trial was discontinued for proteinuria.

Table 5.1.6.7 Patients in the long-term OA/RA trial (024) withdrawn due to renal adverse events^a.

Celecoxib Dose ^b / Patient #	Final Dose	Adverse Event
Celecoxib 200 mg 020-1071	200	Proteinuria, Albuminuria

a. Data from sponsor at reviewer's request submitted 11.3.98.

Conclusion regarding urinary abnormalities

The only urinary abnormality that needs to be discussed is the development of proteinuria. There is no data to suggest an association of celecoxib use with any of the other urinary abnormalities.

The incidence of proteinuria is low in the controlled database. While the routine measurements revealed no increased incidence of proteinuria, there is an increased number of patients in the celecoxib group identified as having proteinuria as an AE. Additionally, there is a nominally significant association between the development of proteinuria and elevated BUN in the celecoxib group. A small number of individuals also had both of these abnormalities at the time of their last clinic visit. Of particular concern are the 3 individuals who began the trial without proteinuria, but developed 2-3+ proteinuria and abnormalities of both BUN and Cr at their last clinic visit. Whether these individuals represent a nephrotoxic insult due to celecoxib is, of course, impossible to determine absolutely. It is also difficult to determine the cause of the proteinuria in the one individual withdrawn from the long-term trial. Without more data it is impossible to determine whether these individuals would have gone on to develop nephrotic syndrome or other hallmarks of NSAID nephrotoxicity.

In conclusion, the data are insufficient to determine whether celecoxib use is associated with an increased incidence of proteinuria. In the subset of patients who developed proteinuria during celecoxib use, however, there is evidence that they may be at risk for the development of decreased renal clearance function (marked by increases in BUN and/or Cr), suggesting a nephrotoxic insult. The clinical implications of this observation are not known.

5.2.3d Changes in Serum Electrolytes

Serum electrolytes were collected both as lab values during clinic visits, and as abnormalities (AEs and SAEs). They will be discussed in sets, beginning with the common cations.

Potassium, Sodium, Calcium

1. The changes in lab values were examined as changes in the mean lab value. There were small, albeit significant, differences between celecoxib and placebo with regard to both final mean potassium (higher in celecoxib) and chloride (higher in celecoxib). During the long-term trial, mean serum K⁺ rose 0.04±0/006 meq/L (table 5.1.4.1.4). No significant changes in either calcium or sodium were detected in any analysis (table 5.1.4.1.2).

From Table 5.1.4.1.3 Mean changes in final measured potassiums in the controlled N.A arthritis trials^a.

Changes in Final Visit Lab Values from Baseline	Placebo	Celecoxib 400 mg	Active Controls	p Value Celecoxib vs. Placebo	p Value Celecoxib vs. Active Cntrl	p Value Active Cntrl vs. Placebo
Potassium (mmol/l)	-0.03±0.02	+0.05±00.02	-0.01±0.02	<0.001	0.013	NS

a. Data from NDA Integrated Safety Summary, table 25.1.2. The database used is from studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087. Number of subjects in each measurement varies between 410 and 440 (see table 25.1.2 for details).

2. The changes in lab values were also examined both as changes from normal (shift-table). Here again, the only significant difference in the controlled arthritis trials was that more subjects in the celecoxib and active control groups developed hyperkalemia at some point during the 12 week trials compared with placebo. Of the patients who started the trial with hyperkalemia, a significant fraction also had hyperkalemia during the trials.

From Table 5.1.4.1.5 Shift in serum potassium values in the 12-week, controlled N.A arthritis trials^a.

Maximal Change in Lab Value	Celecoxib 400 mg	Placebo	Active Controls
Potassium (mmol/l)			
High (5-6 mmol/l)	20/399 from Normal (5.0%) 5/12 from High	8/416 from Normal (1.9%) 2/8 from High	20/419 from Normal (4.8%) 3/9 from High

a. Data from NDA Integrated Safety Summary, table 5.1.2. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

3. The incidence of AEs related to abnormalities of potassium, sodium or calcium were rare, and equal in the three treatment groups. There were no SAEs related to electrolyte abnormalities in the controlled trials.

From Table 5.1.3.1 Adverse events related to cations in the N.A arthritis trials^a.

Metabolic Abnormalities AEs	Placebo N=1864	Celecoxib 25-400 mg N=5704	Celecoxib 100-200 mg N=3512	Active Controls N=2098
Hypercalcemia	1 (<0.1%)	5 (0.1%)	N/A	1 (0.1%)
Hyperkalemia	0 (0%)	5 (0.1%)	3 (<0.1%)	0 (0%)
Hypernatremia	0 (0%)	1 (<0.1%)	1 (<0.1%)	0 (0%)
Hypocalcemia	0 (0%)	2 (<0.1%)	N/A	1 (0.1%)
Hypokalemia	8 (0.4%)	16 (0.3%)	9 (0.2%)	4 (0.2%)
Hyponatremia	4 (0.2%)	2 (<0.1%)	1 (<0.1%)	0 (0%)

a. Data from NDA Integrated Safety Summary, table 6.2 and 31.3.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

4. In the long-term trial there were two SAEs related to electrolytes: hyponatremia and hypokalemia. One of these resulted in patient discontinuation. Both patients developed hyponatremia/hypokalemia during diuretic use concurrently with celecoxib.

From Table 5.1.2.3 Changes in serum potassium identified as SAEs in the long-term celecoxib database^a.

SAEs	Patient #	Age/ Sex	Treatment	Stopped Tx?
Hypokalemia	024-US0013-0130009	78/F	Celecoxib 200 mg BID	No
Hyponatremia	024-US0033-0330007	72/F	Celecoxib 300 mg BID	Yes

a. Data from Integrated Summary of Safety, Text Table 136.

1. Patient #024-US0033-0330007 was a 72-year-old female with history of hypertension, venous insufficiency, hypercholesterolemia, and hypothyroidism. Concurrent medications included hydrochlorothiazide, triamterene, verapamil, and calcium. This patient took celecoxib 300 mg BID for 14 days before discontinuing because of treatment failure. Two days after stopping celecoxib, she was hospitalized with a plasma sodium level of 122 mmol/L. She received IV fluid and her plasma sodium returned to normal. Her hospital diagnosis indicated metabolic encephalopathy secondary to hyponatremia most likely due to diuretic therapy.

2. Patient 024-US0013-0130009 was a 78-year-old female with a history of hypertension, urinary complaints, and elevated liver function tests. Concurrent medications included doxazosin, Moduretic and indapamide. The patient initiated treatment with celecoxib 200 mg BID and experienced sinusitis eight-and-one-half months later. She was treated with antibiotics but three days later she lost consciousness and was incontinent of urine. Following this syncopal episode, she vomited. She was taken to the hospital, where her serum potassium and sodium were found to be 2.9 mmol/L and 132 mmol/L, respectively. She was rehydrated with intravenous solution, treated with potassium, and indapamide was discontinued. Amoxicillin was continued to treat the sinusitis. Her hyponatremia is also presumed to be secondary to diuretic therapy.

5. In the long-term trial, there was one individual who was discontinued for hyperkalemia.

Conclusion regarding sodium, potassium, and calcium lab abnormalities

In the short-term trials, there is a suggestion that celecoxib use may be associated with clinically significant increases in serum potassium in some individuals. These changes were of similar frequency and severity in both the celecoxib and active control groups. The long-term trial had no SAEs related to hyperkalemia, and only one individual withdrawn because of it. In conclusion, while the database is inadequate to establish a possible effect of celecoxib on potassium, leading to hyperkalemia in susceptible individuals.

Chloride and Phosphate/ Disorders of Acid-Base Status

Detection of effects on acid-base status are severely limited by the absence of long-term bicarbonate data. In its absence, one indirect marker for a decreased bicarbonate is an increase in serum chloride. Interpretation of this is limited by the other causes of an increased chloride which do not reflect the development of acidosis (i.e., infusion of anionic solutions, use of acetazolamide and other inhibitors of bicarbonate resorption). These other causes would presumably occur randomly, so that if there is a significant difference in the incidence of hyperchloremia between the three treatment groups in the controlled database this may suggest an adverse effect on acid-base balance.

First, the incidence of abnormalities related to chloride and phosphate will be examined.

1. There was also a significant increase in the mean serum chloride in the celecoxib group in the controlled OA/RA trials, and a decrease in the mean serum phosphate in the active control group, relative to placebo. There was no trend towards a decreased phosphate in the celecoxib group relative to placebo.

From Table 5.1.4.1.3 Mean changes in final measured chloride and phosphate in the controlled N.A. arthritis trials from NDA 20-998^a.

Changes in Final Visit Lab Values from Baseline	Placebo	Celecoxib 400 mg	Active Controls	p Value Celecoxib vs. Placebo	p Value Celecoxib vs. Active Cntrl	p Value Active Cntrl vs. Placebo
Chloride (mmol/l)	-0.2±0.17	+0.3±0.18	+0.0±0.18	0.046	NS	NS
Phosphate (mmol/l)	+0.008±0.009	+0.010±0.009	-0.042±0.008	NS	<0.001	<0.001

a. Data from NDA Integrated Safety Summary, table 25.1.2. The database used is from studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087. Number of subjects in each measurement varies between 410 and 440 (see table 25.1.2 for details).

2. There were also more individuals who developed abnormally high chlorides with normal chlorides at baseline in the celecoxib and active control groups. Celecoxib and placebo had similar incidence of hypophosphatemia (both less than the active control group).

From Table 5.1.4.1.5 Shift in serum chloride and phosphate in the 12-week, controlled N.A. trials for the 400 mg dose group^a.

Maximal Change in Lab Value	Placebo	Celecoxib 400 mg	Active Controls
Chloride			
Low (75-90 mmol/l)	0/0 from Low	0/0 from Low	0/0 from Low
High (110-130 mmol/l)	0/413 from Normal 19/413 from Normal (4.6%) 4/17 from High (23%)	2/408 from Normal 40/406 from Normal (9.8%) 3/13 from High (23%)	5/407 from Normal 45/407 from Normal (11.0%) 12/27 from High (44%)
Extreme High or Low	None	None	None
Phosphate			
Low (0.32-0.97 mmol/l) (1.0 to 3.0 mg/dl)	31/63 from Low (49%) 55/366 from Normal (15.0%)	42/70 from Low (60%) 61/348 from Normal (17.5%)	62/75 from Low (83%) 117/358 from Normal (32.6%)
High (1.61-2.42 mmol/l) (5.0 to 7.5 mg/dl)	3/366 from Normal 2/2 from High	2/348 from Normal 0/0 from High	2/358 from Normal 0/0 from High
Extreme High or Low	None	None	None

a. Data from NDA Integrated Safety Summary, table 5.1.2. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

3. Patients in the celecoxib group were significantly more likely to have serum chloride >110 mmol/l and PO₄ <0.97 mmol/l during the 12 week controlled trials, when compared with placebo.

From Table 5.1.4.2.3 Incidence of abnormal Cl and PO₄ the North American 12-week Arthritis trials.

AE/ Lab Value	Placebo N=1136	Celecoxib 100 mg N=1131	Celecoxib 200 mg N=1125	Celecoxib 400 mg N=434	Active Control N=1099
Chloride >110 mmol/l	48 (4.2%)	88 (8.0%)	88 (7.8%)	87 (8.5%)	82 (7.5%)
Chloride >120 mmol/l	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PO ₄ <0.97 mmol/l ^f	195 (17.2%)	233 (20.6%)	237 (21.1%)	83 (19.1%)	351 (31.9%)

a. Data from data submitted to FDA 10.9.98 from sponsor, and not independently confirmed by FDA reviewer.

Overall, these differences were significant for both chloride and phosphate. There was also a trend towards patients having abnormalities in both chloride and phosphate (but not both abnormalities at the last clinic visit).

Table 5.1.4.2.11. Association between Ca²⁺, PO₄⁻, and Cl⁻ abnormalities in controlled trials^a.

Abnormality	Placebo N=1136	Celecoxib N=2256	Active Control N=1099
PO ₄ <0.97 mmol/l	195 (17.2%)	470 (20.8%)	351 (31.9%)
Chloride >110 mmol/l	48 (4.2%)	178 (7.9%)	82 (7.5%)
Both low PO ₄ and high Cl ⁻	16 (1.4%)	51 (2.3%)	34 (3.1%)
Both low PO ₄ and high Cl ⁻ at last clinic visit	8 (0.70%)	14 (0.62%)	8 (0.73%)

a. Data from analyses performed by sponsor, and not independently confirmed by FDA.

4. Patients in the celecoxib and active control groups were also more likely to have chlorides >113 at the time of their last visit in addition to decreased PO₄.

Table 5.1.4.2.6. Patients in the N.A. OA/RA database with Cl⁻ >113 mmol/l with one or more of the other listed abnormalities at last clinic visit^a.

Patient #	Days on Study Drug	Baseline/ Final PO ₄ ⁻ (mmol/l and mg/dl)	Baseline/ Final Cl ⁻ (mmol/l)
Placebo (n=1136)			
None			
Celecoxib (n=2256)			
022-0861	87	1.16/ 0.81	107/ 115
054-1137	12	0.84/ 0.74 ^b	109/ 115
020-0357	85	1.07/ 0.84	112/ 114 ^b
023-1358	43	0.97/ 0.94	109/ 116 ^c
Active Control (n=1099)			
023-1350	43	0.97/ 0.94	109/ 116
022-1072	81	1.13/ 0.84	110/ 116
023-0389	29	1.03/ 0.87	106/ 115

a. Data from examination of individual line-listings from SAS datasets provided by sponsor.

b. Note that HCO₃⁻ or PO₄⁻ was abnormally elevated at time of entry.

c. This patient also had new, trace proteinuria at last clinic visit.

Patients with hyperchloremia, however, were more likely to also have hypophosphatemia in the celecoxib group, as shown above. The hyperchloremic individuals were not more likely to have experienced an AE related to fractures (accidental or pathological). Such Bony AEs might be expected following long-term metabolic acidosis.

From Table 5.1.4.2.14. Association between hyperchloremia and bony AEs in controlled trials^a.

Abnormality	Placebo N=1136	Celecoxib N=2256	Active Control N=1099
Chloride >110 mmol/l	48 (4.2%)	178 (7.9%)	82 (7.5%)
Fractures, Accidental	3 (0.3%)	10 (0.4%)	4 (0.4%)
Fractures, Pathologic	0 (0%)	0 (0%)	0 (0%)
Myalgias	23 (2.0%)	45 (2.0%)	8 (0.7%)
Both Chloride and one AE	2 (0.2%)	6 (0.3%)	1 (<0.1%)

a. Data from analyses performed by sponsor, and not independently confirmed by FDA.

5. In the long-term trial, 13.2% of the patients had hyperchloremia during their follow-up, of which three had hyperchloremia >113 mmol/l at the last visit.

Table 5.1.4.2.8. Patients in the long-term, open-label trial with Cl⁻ >113 mmol/l with other renal lab abnormalities at last clinic visit^a.

Patient #	Days on Study Drug	Baseline/ Final PO ₄ ⁻ (mmol/l and mg/dl)	Baseline/ Final Cl ⁻ (mmol/l)
012-0504 ^c	366	1.0/ 1.13	112/ 114
022-1433	83	1.10/ 0.90 (low)	109/ 114
022-0861	87	1.16/ 0.81 (low)	107/ 115

a. Data from examination of individual line-listings from SAS datasets provided by sponsor.
c. This patient also had new, trace proteinuria at last clinic visit.

6. Two patients with notable abnormalities in renal labs the long-term trial are summarized below. One had a persistent severe hypophosphatemia with hyperchloremia. The other patient developed proteinuria associated with hypophosphatemia.

Table 5.1.4.2.9. Patients in the long-term, open-label trial with notable renal lab abnormalities^a.

Patient #	Days on Study Drug	Baseline/ Final PO ₄ ⁻ (mmol/l and mg/dl)	Baseline/ Final Cl ⁻ (mmol/l)
022-0622	92	0.55/ 0.42	109/ 113
013-0401 ^c	452	1.58/ 0.94	107/ 106

a. Data from examination of individual line-listings from SAS datasets provided by sponsor.
c. This patient also had 1+ proteinuria at start of trial, which progressed to 3+ at last clinic visit. BUN/Crt were normal at all

time points measured.

7. No patients developed severe hyperchloremia (>120 mmol/l) during either the controlled or open-label trials (tables 5.1.4.2.3 and 5.1.4.2.4).

8. The incidence of AEs related to serum chloride or phosphate was equal in all three treatment groups. Note that only those abnormalities identified by investigators are coded as AEs.

From Table 5.1.3.1 AEs related to PO₄ and Cl⁻ in the N.A. Arthritis trials of celecoxib from NDA 20-998^a.

Metabolic Abnormalities/ AE	Placebo N=1864	Celecoxib 25-400 mg	Celecoxib 100-200 mg	Active Controls
Hyperchloremia	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypophosphatemia	0 (0%)	1 (<0.1%)	1 (<0.1%)	0 (0%)

a. Data from NDA Integrated Safety Summary, table 6.2 and 31.3.2. The database used is from the North American Arthritis trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

9. There were no SAEs or withdrawals related to abnormalities in either serum chloride or phosphate in the controlled trials or in the long-term trial (tables 5.1.2.3, 5.1.6.6, and 5.1.6.7).

10. An analysis of those individuals who received bicarbonate or citrate therapy revealed no increase in their use among the celecoxib group. Where identified, patients received these products for GI reasons primarily, and none was identified as receiving them for systemic acidosis. The use of acetazolamide was also balanced between the treatment groups.

Conclusion regarding chloride and phosphate lab abnormalities

Sufficient data exists to definitely associate the administration of celecoxib and active control with the development of hyperchloremia. The clinical consequences of these lab abnormalities cannot be finally determined without other data (in particular, serum bicarbonates). That rare individuals develop a greater degree of hyperchloremia in the celecoxib group than is seen in the placebo is consistent with a true effect, as opposed to a statistical oddity. Unfortunately, we have no database from other NSAIDs at this time to gauge whether these effects are more or less common with celecoxib compared with other NSAIDs. If we use the active control group data, the effect of celecoxib on serum chloride is numerically similar to the active controls.

With regard to hypophosphatemia, we are again faced with a lab abnormality definitely associated significantly with celecoxib (and especially with active control) without clear clinical consequences. There was no increase in bony fractures in those individuals with hyperchloremia or hypophosphatemia, as might be expected if there is a change in the acid-base balance. An increase in bony fractures has been seen with other drugs with prominent renal tubular toxicities resulting in renal tubular acidosis. The controlled trials were also too short to examine the rate of renal stone formation, which might also increase during renal tubular acidosis.

In conclusion then, the best evidence suggests that the observed changes in chloride reflect true effects of both celecoxib and the active controls used. The less robust association between celecoxib administration and hypophosphatemia is less more difficult to interpret, but the pattern of effects for celecoxib on phosphate can be distinguished from the placebo group. The clinical implications of these lab abnormalities, including the possibility that the changes in serum chloride may reflect some alteration in the acid-base balance in certain individuals, simply cannot be determined with the available data.

5.3 Recommendations of Renal/ Cardiac Consultant

General Summary

During the development of specific inhibitors of the type 2 isoform of cyclooxygenase (COX-2), it was hoped that they would provide selective anti-inflammatory/ analgesic efficacy without concomitant GI and renal toxicity. This was based on animal work that suggested that the GI system and kidneys did not express the COX-2 isoform. More recent work has demonstrated the clear presence of COX-2 in the kidney, both in normal human and animal kidneys and in patients with systemic lupus erythematosus (ref. 3). Work in animals has also suggested the up-regulation of COX-2 following volume contraction (ref. 1, 2). These data suggest, at the very least, that the target of COX-2 inhibitors is present in the kidney. That this target (COX-2) may be increased during times of sodium- and water-depletion suggests a role for COX-2 in protecting renal hemodynamics. Whether these observations translate into an increased risk of nephrotoxicity in clinical states associated with impaired renal perfusion, such as volume contraction, is not known at present.

Cardiac and renal safety was examined in both the short-term, controlled trials, and in the longer, open-label trial of patients with osteoarthritis/ rheumatoid arthritis (OA/ RA). Overall, 6376 patients were exposed to celecoxib during the short-term, controlled, North American trials in OA/ RA. During the open-label trials, another 9822 patients received celecoxib. Of these, the large majority received drug for <180 days. For long-term exposure, 1809 OA/ RA patients received celecoxib for periods lasting for between 12 weeks and > 1 year in an open-label trial.

As part of the safety database, the sponsor collected adverse events related to both clinical and laboratory measurements. In addition, serial laboratory measurements were obtained from a subset of patients. Significantly, no measurements of acid-base balance were performed as part of any trial in the NDA database (e.g., serum bicarbonate, arterial pH). With this exception, the database was sufficient to assess the majority of the clinically relevant renal and cardiac toxicities.

Cardiac Safety

The administration of celecoxib cannot be linked to any rare or unusual cardiac toxicities based on the available data. For some adverse events, including arrhythmias and overall cardiovascular mortality, the data are inadequate to either exclude or confirm an adverse effect of celecoxib.

With regard to cardiovascular adverse events, there is a probable association between celecoxib administration and worsened hypertension in susceptible individuals. This effect of celecoxib resembles that of other non-steroidal anti-inflammatory drugs (NSAIDs). There is also a probable association between celecoxib administration and the development of clinically significant edema, again similar to other NSAIDs.

In summary, the available data suggest that the effects of celecoxib are similar to other NSAIDs with regard to 'cardiac' effects: hypertension and edema. The data also suggest that both celecoxib and the comparator NSAIDs are clearly distinguished from placebo with regard to the incidence of both hypertension and edema. As is common with NDA databases of this size, the data are inadequate to exclude significant effects of celecoxib and NSAIDs on some aspects of cardiac safety, including overall cardiac mortality.

Renal Safety

Three trials were performed on specific populations (elderly patients, patients with mild-to-moderate renal insufficiency, patients with volume contraction) to examine their renal responses to celecoxib. These trials examined the short-term effects of celecoxib on the excretion of prostaglandins, as well as a variety of other renal parameters. Given the small numbers of patients, the short trial durations, and the broad patient-patient variability, the broadest conclusion is that, under the conditions of those trials, both celecoxib and the comparator NSAIDs has significant inhibitory effects on the excretion of the urinary prostaglandins when compared with placebo. In particular, celecoxib and the comparator NSAIDs inhibit prostaglandin PGE₂ and 6-keto-PGF_{1- α} excretion by the kidney to more or less the same extent over the duration of the individual trials.

Renal Safety (cont)

With regard to the renal safety database, three outcomes were possible from the data.

1) The first was that all three treatment groups (placebo, celecoxib and comparator NSAIDs) would show similar patterns of renal effects, including lab abnormalities and clinical adverse events. In this case, a reasonable conclusion would be that the database was underpowered, as it was not able to differentiate between placebo and the active control NSAIDs, which have-known renal toxicity.

2) The second possibility is that both celecoxib and the comparator NSAIDs were differentiated from placebo, and more or less resembled each other as regards renal effects. This is the pattern seen in the NDA.

3) The final possibility is that celecoxib would most closely resemble placebo, and that both would be clearly distinguished from the comparator NSAID group.

There is sufficient evidence to conclude that both celecoxib and the comparator NSAIDs have similar renal effects. First, this is reflected in the increased incidence of several lab abnormalities during celecoxib and comparator NSAID administration, when compared with placebo: hyperchloremia, hypophosphatemia, and elevated BUN. These surrogates for renal toxicity suggest, but do not confirm, a link between celecoxib use and clinically relevant nephrotoxicity.

The similarity of celecoxib and the comparator NSAIDs is also suggested by the association their use with an increased incidence of reported edema and worsened hypertension, when compared with placebo. The data suggest that these adverse events occur at a similar rate in patients receiving celecoxib and the comparator NSAIDs, and at a higher rate than in placebo-treated patients.

Finally, the pattern of more severe clinical renal adverse events is similar to the pattern expected for NSAIDs, and different from the pattern seen in the placebo group. This includes those renal adverse events causing withdrawal from the trials and the reported renal serious adverse events. There were no cases of severe renal injury detected in the celecoxib group: nephrotic syndrome, papillary necrosis, or interstitial nephritis. Given what is known about the rarity of these events following NSAID use, this absence should be attributed to the low event rate, and does not mean that they might not occur. There were several individuals on celecoxib in the long-term, open-label trial who were withdrawn because of renal adverse events, including acute renal failure (as well as edema and worsening hypertension). While a direct link between events in open-label experience and celecoxib use cannot absolutely be made with the available data, they are consistent with the patterns of clinical renal disease seen with other NSAIDs.

Within the limitations of the database there is no evidence to suggest that celecoxib has unique renal or cardiac toxicities not shared with other NSAIDs, and no evidence of a toxicity caused by other NSAIDs that occurs at a significantly higher incidence rate with celecoxib. In the absence of bicarbonate data, an adverse effect of celecoxib on acid-base balance cannot be excluded, particularly in the context of the observed increase in hyperchloremia and hypophosphatemia.

In conclusion, the available data suggest that celecoxib resembles other NSAIDs in the majority of the renal effects examined in the NDA. Further, the available data suggest that the renal effects of celecoxib and the comparator NSAIDs are clearly distinguished from placebo. It remains to be determined is whether severe renal injury will occur during celecoxib use at the same rate as with other NSAIDs.

5.3.1 References

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