NDA No. 20-998
CELEBREX® (Celecoxib 100 mg, 200 mg, 400 mg)

Celebrex Capsules
(Celecoxib)

NDA 20-998

Medical Officer Review

Submission Date:	June 29, 1998
Received Date:	June 30, 1998
Review Date:	July 8, 1998
Drug Name:	Celebrex™
Generic Name:	celecoxib
Applicant:	G.D. Searle & Co. 4901 Searle Parkway Skokie, IL 60077
Pharmacologic category:	COX-2 inhibitor
Proposed Indication:	Management of: • pain • rheumatoid arthritis • osteoarthritis
Dosage forms and route:	Oral capsule, 100 and 200 mg
Submission type:	Original NDA

Orig NDA # 20-998
HFD-550/Div File
HFD-550/PM/Lutwak
HFD-550/Pharm/Yang
HFD-550/Chem/Bhavnagri
HFD-550/Biopharm/Bashaw
HFD-550/Statistics/Lin
HFD-550/MO/Witter

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(James Witter, M.D., Ph.D. Medical Officer)

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Celecoxib Executive Summary

Significant Issues

- If approved, celecoxib would be the first so-called "COX-2 selective" agent approved in the U.S. In fact, as noted below, it is suggested that celecoxib be called a "specific" COX-2 inhibitor. The biological and clinical implications of this designation are, at present, not fully characterized.

- Although the single-dose, dental pain trials have established that celecoxib is efficacious compared to placebo, the other postsurgical pain trials did not confirm the analgesic properties of the proposed doses.

- Because serum bicarbonates were not measured, the NDA database cannot exclude an adverse effect of celecoxib on acid-base balance.

- Celecoxib is efficacious in the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis at the proposed doses.

Highlights

- Endoscopic data with celecoxib have found that it is associated with significantly fewer endoscopically-defined ulcers as compared to studies with ibuprofen and naproxen. However, celecoxib was associated with fewer ulcers in only one of two such endoscopic studies with diclofenac. However, these ulceration rates are not equivalent to placebo.

- The overall safety profile of celecoxib suggests at this time that it is generally more comparable to NSAIDs (ibuprofen, diclofenac, naproxen) than to placebo.

- Randomized and open-label trials, to date, suggest the rate for clinically relevant upper gastrointestinal events is less with celecoxib than that of traditional NSAIDs.

- If approved, celecoxib would be the first compound with properties similar to currently understood NSAIDs to successfully employ the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index as well as the American College of Rheumatology (ACR-20) Responder Index for rheumatoid arthritis in a New Drug Application.

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BACKGROUND AND OVERVIEW:

Celecoxib (Cx) is the USAN name for 4-[5-(methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide which is a diarylsubstituted pyrazole compound. The trade name for this same compound is ***Celebrex*** while the code name is ***SC-58635.*** Cx was originally developed as a "selective" prostaglandin G/H synthase-2 (i.e. ***COX-2***) inhibitor. However, during the development of this compound, Cx is now presented as a "specific" COX-2 inhibitor (SCI). According to current thinking, such "SCI inhibitors" at therapeutic doses would inhibit COX-2 and would be maximally effective in treating inflammation and pain, but would not inhibit COX-1 activity involved in normal physiologic function (see below). Many regard this compound as a new class of anti-inflammatory and analgesic agents. In fact, the WHO has recently changed the ATC classification of Cx to "COX-2 specific inhibitors".

From studies dating back only to the late 1980's and early 1990's, it became clear that there must be another isoform of human cyclooxygenase (COX), the enzyme which catalyzes the rate-limiting step in converting arachidonic acid to prostaglandins (PG), thromboxanes, and leukotrienes. For example, early experiments with endotoxin-treated monocytes showed that the significant increase in PGE_2 was inhibited by dexamethasone, this corticosteroid is not known to alter the transcription of COX-1. Subsequently, the theory has evolved that COX-1 and COX-2 may subserve different roles in the body. Originally, COX-1 was postulated to be a constitutive form of COX involved in "house-keeping" functions, such as maintenance of the gastrointestinal (GI) tract mucosal integrity, normal platelet function, and renal function while COX-2 represented the inducible form of COX involved in inflammation and pain. Similarly, it was postulated early that COX-1 was present in all cells (and, most importantly, in platelets) while COX-2 was only distributed at sites of inflammation, such as arthritic joints; COX-2 was not present in platelets (since they lack the transcriptional machinery necessary to produce this inducible enzyme).

Currently, it is appreciated that the COX story is much more complicated, and potentially much more interesting. For example, it is now accepted that COX-2 can also be constitutively expressed in areas like the kidney and brain whereas previously these areas were felt to be devoid of any significant COX-2. The situation of whether COX-2 is present in the human GI tract has also rapidly evolved in the last few years. Early on, it was felt that COX-2 was not present in the human GI tract. It is now clear that this enzyme is not only present in the lower GI tract, it is a target for prophylactic therapy of colonic cancer. Similarly, COX-2 is also recognized to be increased in the upper GI tract in situations of ulcer healing or infection with Helicobacter pylori infection. Conversely, there is an understanding that COX-1 can also be inducible under certain experimental

systems and COX-1 may be upregulated in situations when COX-2 is absent or blocked; animals models have been particularly illustrative in this regard. Finally, it is becoming evident that COX-2 may also play important roles in Alzheimer's disease, cardiovascular disease, angiogenesis, along with their already recognized important roles in inflammation, pain and pyrexia.

While on the surface, NDA 20-998 might appear to represent just another drug to review, in reality one could easily argue it represents a test to the various hypotheses of the proposed roles of COX-2 in human health and disease. While reviewing this NDA, the reader is therefore encouraged to constantly question whether we are testing a drug, a theory, or both with this compound? It will be of interest to see where this NDA positions itself in the future in terms of helping to address some of these very important biological and clinical questions.

A total of 51 trials were submitted to support NDA 20-998. As detailed in the Table 1 below, these 51 trials have been divided by the Sponsor into three basic types of studies (Phase 1, Arthritis, Postsurgical Analgesia):

Table 1. Studies Included in NDA 20-998

TYPE OF STUDY	NO. OF STUDIES	STUDY NUMBERS
Phase 1		
Single dose	9	001, 006, 009, 018, 019, 037, 044, 084, 088
Multiple dose	11	003, 004, 010, 014, 015, 026, 032, 033, 043, 065, 069
Drug Interaction	7	017, 038, 039, 040, 050, 051, 072
Hepatic Impairment	1	016
Renal Impairment	1	038
Arthritis		
OA		
Pivotal Efficacy	5	020, 021, 054, 060, 087
Supportive	3	042, 013, 047
RA		
Pivotal Efficacy	2	022, 023
Supportive	2	041, 012
OA/RA combined	2	062, 071
Long-term open label	1	024
Postsurgical Analgesia		
Dental pain		
Pivotal Efficacy	3	025, 027, 070
Supportive	1	005
Surgical Pain		
Pivotal Efficacy	1	028
Supportive	2	029, 080
Total	51	

Reviewer's comment: To facilitate review of the clinical aspect of this NDA, several different Divisions within CDER have been engaged as follows:

Mickey Averbuch, M.D.	Pain trials
Lawrence Goldkind, M.D.	UGI safety
Douglas Throckmorton, M.D.	Renal Safety
Lourdes Villalba, M.D.	General Safety

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Lilia Talarico, M.D. Platelet Safety

While these other reviews have addressed the safety and efficacy of Cx, the consultant reviews outside the Division have focused on platelet effect and function, along with the effects of Cx on the GI tract and kidneys. This review will attempt to integrate the highlights of all these critically important consultant reviews but the interested reader is referred to the original reviews for in-depth details.

Integrated Summary of Safety:

This ISS is not intended to be the only review of the safety of Cx; it is more of a supplement and overview. This relates to the nature of the compound and how the review of this NDA was divided. Celecoxib was developed primarily to address the issue of the UGI safety of NSAIDs. It is well known that NSAIDs are a significant source of UGI morbidity and death. For example, recently updated numbers from the ARAMIS Postmarketing Surveillance Program at Stanford University (Am. J. Med., Vol. 105, [1b] p. 31-38S; July 27, 1998) state that: "Conservative calculations estimate that **approximately 107,000 patients are hospitalized** annually for nonsteroidal anti-inflammatory drug (NSAID)-related gastrointestinal (GI) complications and **at least 16,500 NSAID-related deaths occur each year among arthritis patients alone."** This is stated in another way in the NSAID GI warning template for the Agency which states: "It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients for one year". Therefore, the safety review of the this NDA has been addressed as follows and the interested reader should also see these other reviews:

Maria Lourdes Villalba, M.D.	Celecoxib Safety Review
Larry Goldkind, M.D.	UGI Safety Review
Lilia Talarico, M.D.	Platelet Safety Review
Douglas Throckmorton, M.D.	Renal/Cardiovascular Safety Review

Renal Safety:

Reviewer's comment: For a detailed examination of the results of Cx on renal function and safety, the interested reader is encouraged to read the cardiorenal consult.

Experimental and clinical evidence demonstrates that NSAIDs reduce renal function when renal perfusion is dependent on prostaglandin formation. Patients at risk for acute ischemic renal failure (renal decompensation) include those with a variety of renal diseases, congestive heart failure, cirrhosis with ascites, volume depletion and diuretic use. These effects are normally readily reversible upon withdrawal of the drug. NSAIDs can also produce fluid retention leading to edema formation, interfere with the blood pressure-lowering effects of certain antihypertensive medication and rarely lead to chronic renal injury such as interstitial nephritis or papillary necrosis.

Cyclooxygenase activity can be found throughout the kidney although enzyme activity is most abundantly expressed in four discrete sites; the glomerular afferent and efferent arterioles, the glomerulus, the interstitial cells of the renal medulla and the medullary collecting ducts. It remains unclear how much of renal prostaglandin synthesis is normally mediated by COX-1 or COX-2 at these various sites. COX-2 may be needed for normal development of the kidney during embryogenesis because homozygous COX-2 knockout mice develop kidneys with abnormal nephrons containing hypotrophic glomeruli and dysplastic tubules. Several studies have detected apparent constitutive expression of COX-2 within the kidney at the following level locations:

- macula densa
- interstitial cells of the papillae
- medullary interstitial cells
- epithelial cells of the thick ascending loop of Henle
- glomerular podocytes

These findings suggest COX-2 has a role in handling sodium and in the regulation of both
glomerular filtration and fluid balance. However, it is also highly likely that COX-1, more
ubiquitously distributed in the kidney, plays a significant role in all of these processes too.

Whether COX-2 inhibitors would avoid many of the common NSAID-associated renal toxicities was examined in this NDA.

The three clinical pharmacology studies outlined in table 31, were conducted in selected groups of subjects and patients felt to be at risk for adverse renal hemodynamic effects or excretory changes related to use of NSAIDs.

Table 31. Studies to Assess Effects on Renal Function in NDA 20-998

Study	Population	Treatment Groups and Regimens	Treatment Period	Outcome Measures
010 (n=29)	**Healthy elderly subjects**	**- Celecoxib 200/400 mg BID - Naproxen 500 mg BID Celecoxib 200 mg BID for five days followed by 400 mg BID for 4.5 days, or naproxen 500 mg BID for 9.5 days; after 7 day washout, crossover to opposite treatment**	**10 days**	**Glomerular filtration rate, urinary PGE2 and 6-keto-PGF1$_\alpha$ excretion**
033 (n=42)	**Sodium depleted healthy male subjects**	**- Placebo - Celecoxib 200 mg BID - Celecoxib 400 mg BID - Naproxen 500 mg BID**	**6.5 days**	**Glomerular filtration rate, urinary PGE2 and 6-keto-PGF1α excretion, renal blood flow, plasma renin activity, plasma aldosterone, plasma atrial natriuretic peptide, serum TxB2, fractional sodium,**

				potassium and lithium excretion
036 (n=75)	**Patients with chronic renal insufficiency**	**- Placebo - Celecoxib 200 mg BID - Naproxen 500 mg BID**	**6.5 days**	**Glomerular filtration rate (inulin), urinary PGE2 and 6-keto-PGF1D excretion, plasma renin activity, urinary 11-dehydro-TxB2 excretion, serum TxB2, creatinine clearance, fractional sodium and potassium excretion**

From Text Table 121, ISS.

Principal outcome measures in these studies included glomerular filtration rate (GFR, determined using Glofil, sinistrine, or inulin, and measurement of urinary prostaglandins). Creatinine clearance measurements were also performed as part of two other studies Measurement of prostaglandins in urine has gained general acceptance as a marker of
renal prostaglandin production following the original report suggesting their renal origin in healthy women, although a number of methodologic as well as biologic variables can affect urinary prostaglandin measurements in humans. Urine concentrations of PGE_2 and 6-keto-$PFG_{1\alpha}$ were determined using a combination of chromatographic and GC/ENCI/MS/MS analyses (sensitivity limit of 10 pg/mL) in Studies 010, 036 and 033. Adequate pre-study control assays were conducted to determine accuracy, specificity, sensitivity, and reproducibility of assays. Urine samples were analyzed for 11-dehydro-TxB_2 concentrations using radioimmunoassay competition binding assays. The range of calibration was 10 pg/mL to 1000 pg/mL.

The data suggest that COX-2 is present in the human kidney and so represent a potential and plausible candidate to explain any observed clinical toxicity. Cardiac and renal safety was examined in both the short-term, controlled NA trials and in the longer, open-label trial involving approximately 7400 patients with OA and RA. As part of the safety database, the sponsor collected AEs related to both clinical and laboratory measurements. In addition, serial laboratory measurements were obtained from a subset of patients.

The results (safety, pharmacodynamic) of these trials can be summarized as follows (see cardiorenal consult for details):

1. **No measurements of acid-base balance (e.g. serum bicarbonate, arterial pH) performed as part of any trial in the NDA. Therefore, an adverse effect of Cx on acid-base balance cannot be excluded, particularly in the context of the observed increase in hyperchloremia (see below).**
2. **Both Cx and comparator NSAIDs (in short-term trials) inhibited prostaglandin PGE_2 and 6-keto-$PFG1\alpha$ excretion by the kidney to more or less the same extent. Both had significant inhibitory effects on the excretion of urinary prostaglandins when compared to placebo. Cx caused slightly less of a decrease in GFR in one study (010). Both Cx and naproxen inhibited serum renin and urinary (11-dehydro-TxB2) thromboxane levels.**
3. **There was an association between Cx administration and the development of clinically significant edema (especially peripheral edema), similar to comparator NSAIDs, and clearly distinguished from placebo. Both naproxen and Cx cause sodium retention.**

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

4. **There was an association between Cx administration and the development of worsened hypertension in susceptible individuals, again similar to NSAIDs, and clearly distinguished from placebo.**
5. **There is a definite association between Cx use and an increased incidence of hypophosphatemia, and hyperchloremia compared to placebo and similar to active controls. There was no increase in bony fractures in those individuals with these abnormalities, 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. The clinical consequences of these changes remain to be determined.**
6. **There was a trend towards an increase incidence of elevated serum creatinine values and elevated BUN with proteinuria in both the Cx and active control groups relative to placebo. These surrogates for renal toxicity suggest, but do not confirm, a link between Cx use and clinically relevant nephrotoxicity similar to NSAIDs.**
7. **There is no evidence to suggest that Cx has unique renal toxicities not shared by NSAIDs, or evidence of a renal toxicity caused by NSAIDs that occurs at a significantly higher incidence rate with Cx.**
8. **The pattern of AEs reported in both the controlled and the long-term trials is similar to that expected for NSAIDs.**
9. **There were several individuals taking Cx who were withdrawn from the long-term trials because or renal AEs including acute renal failure, edema and worsened hypertension.**
10. **While there were no clear cut cases of Cx-induced renal failure requiring dialysis, it remains to be determined whether severe renal injury will occur at the same rate that is seen with NSAIDs.**
11. **The renal effects of Cx are clearly distinguished from placebo.**
12. **The NDA does not reveal a strong signal pointing towards substantial clinically serious renal disease (i.e. large numbers of patients with acute renal failure requiring dialysis, nephrotic syndrome, papillary necrosis, interstitial neprhritis). This will require a larger database.**

Cardiovascular Safety

Reviewer's comment: For a detailed examination of the results of Cx on cardiovascular safety, the interested reader is encouraged to read the cardiorenal consult.

The association of COX inhibitors with cardiovascular disease is based on their effects upon prostaglandins, primarily in the kidney, but also to a lesser extent, in platelets and in vascular endothelium. It had been hypothesized that these effects are mostly due to inhibition of COX-1, resulting in fluid retention and hypertension. However, as noted in the cardiorenal consult, Cx is also associated with edema and worsened hypertension. As discussed in one of the consults from the Division of GI and Coagulation Drug Products, Cx does not seem to affect platelet function (aggregation) at, and above, therapeutic doses

This cardiovascular effects of Cx were addressed by following W.H.O.a.r.t. body systems: General Cardiovascular Disorders, Heart Rate and Rhythm Disorders, Myo/Endo/Pericardial and Valve Disorders and Vascular (Extracardiac Disorders). In addition, pertinent adverse events from other body systems, such as hypertension, were reviewed. Serious cardiovascular events, the effects of medical histories and concurrent medications, pertinent vital sign and laboratory data were also reviewed.

Adverse Events
Table 42 below presents the cardiovascular adverse events for which there was a ≥1% incidence in the NA arthritis trials.

Table 42. Cardiovascular AEs: Incidence ≥1% in North American arthritis trials[1]

		Celecoxib (mg)					
Adverse Event	**Placebo**	**50 BID**	**100 BID**	**200 QD**	**200 BID**	**400 BID**	**Active Control**
No. Treated	**1864**	**690**	**1779**	**453**	**1914**	**615**	**2098**
Any event	**53 (3.0)**	**27 (3.9)**	**74 (4.2)**	**22 (4.9)**	**123 (6.4)**	**39 (6.3)**	**120 (5.7)**
Edema peripheral	**21 (1.1)**	**15 (2.2)**	**27 (1.5)**	**13 (2.9)**	**49 (2.6)**	**15 (2.4)**	**45 (2.1)**
Hypertension	**5 (0.3)**	**2 (0.3)**	**11 (0.6)**	**1 (0.2)**	**20 (1.0)**	**3 (0.5)**	**14 (0.7)**

1. From Table 32.1.1 (ISS). Includes trials 012, 013, 020, 021, 022, 023, 047, 054, 060, 062, 071, and 087.

As can be seen, peripheral edema was the most common cardiovascular adverse event. There is no obvious dose-response relationship; overall incidence with Cx appears similar to the active control. Further analysis, (Text Table 154, ISS) revealed there was no statistically significant difference in incidence of peripheral edema between Cx and active control, but there was between Cx and placebo (p=0.007). The peripheral edema associated with Cx was reported as mild to moderate in severity in 97% of cases, and in only 17% was judged to be "probably related" by the Investigator. Of note, generalized edema, a potentially more meaningful indication of clinically important fluid retention (which was coded only when CRF text stated "generalized" or "body" edema), was significantly more frequent in patients receiving active controls than in Cx patients (active control 0.5% vs. 0.1% for Cx, p=0.031). The differences in the incidence of hypertension between treatment groups (in this comparison) was not statistically significant for Cx vs. placebo or for Cx vs. active control. A related, but less frequent, adverse event, "hypertension aggravated" also was also not significantly different in incidence between Cx and placebo, or Cx and active control in these comparisons. There were no events for which there was a ≥1% incidence in any treatment group for patients who withdrew due to a cardiovascular adverse event.

The next table (from Text Table 155, ISS) summarizes the incidences of cardiovascular AEs by body systems and by time interval in the long-term, open-label trial (024).

Table 43. Cardiovascular AEs: Incidence ≥1% in Long-Term Trial (024)[1]

Adverse Events		**Dosing Intervals (Days)**					
	No.(%) of Pts with Event	**1-90**	**91-180**	**181-270**	**271-360**	**361-450**	**451-540**
No. treated	**4499**	**4499**	**3545**	**2373**	**1576**	**970**	**294**

Adverse Event							
Hypertension	**77 (1.7)**	**0.8**	**0.5**	**0.6**	**0.5**	**0.4**	**0.0**
Edema peripheral	**172 (3.8)**	**2.6**	**0.9**	**0.7**	**0.7**	**0.1**	**0.0**
WHO art body system/disorder							
Cardiovascular, general	**29 (0.6)**	**0.2**	**0.2**	**0.2**	**0.5**	**0.0**	**0.0**
Heart rate/rhythm disorders	**65 (1.4)**	**0.8**	**0.4**	**0.4**	**0.4**	**0.3**	**0.0**
Myo/end/pericardial and valvular disorders	**58 (1.3)**	**0.6**	**0.5**	**0.4**	**0.5**	**0.3**	**0.0**
Vascular (extracardiac)	**57 (1.3)**	**0.5**	**0.4**	**0.6**	**0.3**	**0.2**	**0.0**

1. From Tables 9.2 and 9.5 (ISS).

As with many other adverse events in this trial, the highest incidence of peripheral edema occurred in the first 90 days of dosing with celecoxib, during which time the patients were seen more frequently than in later intervals. Peripheral edema was, however, the only cardiovascular adverse event for which there appeared to be a temporal relationship to the onset of dosing. The prevalence of peripheral edema remained essentially constant at 2.6% throughout the first year in the trial, and fell slightly to 1.7% at 451-540 days. The cases of peripheral edema resulted in a low incidence of withdrawals (<0.1%) for all treatment intervals (Table 9.6, ISS).

The only cardiovascular-related AEs that occurred in ≥1% in the international arthritis trials were hypertension and peripheral edema (hypertension, 0.9-1.2% with Cx vs. 0.0-1.5% with active controls: peripheral edema, 2.0-3.4% with Cx vs. 1.5-2.3% with active controls).

> Reviewer's comment: Serious adverse events, withdrawals and deaths related to the cardiovascular system as well as potential interactions with various drugs classes (i.e. ACE inhibitors, beta blockers, etc.) are discussed in detail in the cardiorenal consult.

Comparison of increases in BUN and creatinine (Cr) have been useful screens to help evaluate the overall potential for a drug to cause damage (reversible or not) to the kidney. In the NDA, evaluation of increases of these laboratory values has resulted in the following (Table 44):

Table 44. BUN (mmol/L) by Creatinine (Cr -μmol/L) Contingency Table[a]

Increase of:	Percent of Patients: Controlled Trials[b] (n)			Open-Label
	Cx (5538)	**Active Control (2025)**	**Plc (1786)**	**Cx (4404)**
Cr < 159 and BUN ≥ 14.3	**0.3**	**0.2**	**0**	**0.2**
Cr ≥ 159 and BUN ≥ 14.3	**0.04**	**0.15**	**0.06**	**0.18**

a.) Data from Table 4.1 (N49-98-17-819)

b.) **Includes studies 012, 013, 020, 021, 022, 023, 041, 042, 047, 054, 060, 062, 071 and 087.**

These results are consistent with that of the other renal safety results which suggest that, overall, event rates for potentially serious events are low but that Cx is more like the active control than placebo in this regard.

The overall cardiovascular safety profile of Cx is mostly unremarkable. However, the increased rate of peripheral edema compared to placebo (2.1% vs.1.1%) are real and are similar to the incidence seen with active control (2.1%). This edema was generally mild, and usually not attributed to treatment by the Investigator. The edema did not appear to be significantly associated with or exacerbated by preexisting cardiovascular disease or use of concomitant cardiovascular medications.

In conclusion, as noted under the "Deaths" section of this review, and in the cardiorenal consult, myocardial infarction was noted to occur at a higher rate in Cx than placebo patients. In the long-term trial, the predominate (90%+) cause of death for patients taking Cx at any dose was cardiovascular. The majority of these deaths represented progression of previously known CV disease. The demographics of the subjects in the controlled trials, as estimated from ICD-9 codes, reveals that about 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. Examination of the Kaplan-Meier survival curves (see cardiorenal consult) for both the controlled and long-term trials, suggests there is no apparent relationship between any given duration of exposure to Cx and increased mortality.

Nonetheless, there may are suggestions of a dose-response relationship between CV mortality and Cx use although the database is not sufficient to answer this question either way. It is interesting to remember, however, that Cx is not associated with antiplatelet effects. Therefore, it seems reasonable to remind physicians that Cx does not provide cardiovascular prophylaxis. Cardiovascular serious adverse events, withdrawals, vital signs and clinical laboratory test parameters abnormalities were unremarkable with Cx and did not seem to indicate any pattern of drug association.

The administration of Cx cannot be linked to any rare or unusual cardiac toxicities based on the available data. For some AEs, including arrhythmias and overall CV mortality, the data are inadequate to either exclude or confirm and adverse effect of Cx. The available data do suggest the effects of Cx are similar to NSAIDs with regard to the "cardiac" effects of hypertension and edema (see Renal Safety section).

Deaths:

Reviewer's comment: Interested readers should read the extensive discussion of this topic in the cardiorenal consult.

In the Cx program to date, which includes the 120 day safety update (letter date: October 28, 1998, cutoff date of update: July 24, 1998)), there have been a total of 44 deaths which are summarized in table 52.

Table 52. Disposition of Deaths in the ISS and Safety Update

	Reported in ISS		New Reports in Safety Update		Cumulative Total	
	Cx	Active Control	Cx	Active Control	Cx	Active Control
Controlled arthritis trials	**4**	**4**	**0**	**0**	**4**	**4**
Pain Studies	**0**	**0**	**0**	**1***	**0**	**1**
Long-term open label study	**18**	**-**	**6**	**-**	**24**	**-**
Ongoing/other studies	**1**	**1***	**0**	**0**	**1**	**0**
Surgical pain 075	**0**	**0**	**1b**	**1b**	**1b**	**1b**
Surgical pain 082	**0**	**1***	**-**	**-**	**-**	**-**
Open label 058	**1**	**-**	**-**	**-**	**1**	**-**
Alzheimer's 1Q5-001	**6b**	**6b**	**2b**	**2b**	**8b**	**8b**
Chemoprevention 1Q4-001	**1b**	**1b**	**-**	**-**	**1b**	**1b**
Subtotal	**23**	**5**	**6**	**0**	**29**	**5**
Blinded (b)	**7**		**3**		**10**	
Grand Total	**35**		**9**		**44**	

*** This death in study 082 was reported as a death in an ongoing study in the ISS; it is now counted as a death in a completed surgical pain study, but not added to the total of new reports in the Safety Update.**

As can be seen, although 35 deaths were reported in the ISS, 26 of them are described further both below and/or in the renal safety consultation. Of the 9 new deaths reported in the Safety Update, six will be described briefly. Since the cutoff date for the Safety Update was July 24, 1998, there were three additional deaths noted in Text Table 18 of the Safety Update that occurred during the treatment between July 25, 1998 and September 11, 1998. These patients are summarized as follows:

- **Pt number (024-US0007-007051); DER Number (970912-CL896). 63 y/o female taking Cx 300 mg BID on 67. Cause of death listed as carcinoma.**
- **Pt number (024-US0090-090028); DER Number (980917-CL561). 61 y/o male taking Cx 100 mg BID on day 327. Cause of death listed as MI.**
- **Pt number (024-US121-121022); DER number (980910-CL790). 63 y/o male taking Cx 400 mg BID on day 496. Cause of death listed as unknown.**
- **Pt number (024-US0015-0150041); DER number (980527-CL495). 58 y/o female taking Cx 400 mg BID on day 614. Cause of death listed as ventricular fibrillation/aortic stenosis.**
- **Pt number (024-US0211-2110005); DER number (980702-CL081). 65 y/o male taking Cx 200 mg BID on day 244. Cause of death listed as CHF.**
- **Pt number (0870092). 75 y/o male taking 300 mg BID on day 414. Cause of death listed as cancer.**

Reviewer's comment: Therefore, it appears that the total number of deaths in patients taking Cx as of the writing of this review is 29. Eighteen (18) were in study 024, four (4) in the controlled trials and one (1) in the other studies listed- all of these 23 patients were reported in the ISS. The six (6) additional deaths

were in the Safety Update and they are listed above in the bulleted items.

As noted in table 52, six of these new deaths occurred in the long-term, open label study and three occurred in two ongoing (blinded) trials.

Is should be noted that NONE of these deaths were considered by the Searle Safety Monitor or the panel of safety consultants to have been related to study medication.

There were 26 deaths in patients who participated in studies included in the NDA. A narrative listing of all of the deaths is to be found in Appendix two of this consult. A total of eight subjects who enrolled in controlled arthritis trials died. Six deaths occurred during controlled arthritis studies, and two following discontinuation of study drug. Four of the individuals in the controlled arthritis group who died received celecoxib, while four received active control drug. The individuals in bold letters died of cardiovascular disease.

Table 53. Deaths: Controlled Trials in the NDA 20-998[a]

Subject #	Age/ Sex	Treatment	Duration of Tx	Cause of Death
Deaths During Study Drug Administration				
041-BE0002-0010	70/M	Celecoxib 200 mg BID	81	Gallbladder carcinoma with liver metastasis
062-US0117-46761235	**68/M**	**Naproxen 500 mg BID**	**63**	**Brain-stem infarct**
071-US0382-65811310	78/M	Ibuprofen 800 mg TID	29	Obstructive pulmonary disease
071-US0333-46521451	**53/F**	**Diclofenac 75 mg BID**	**1**	**Hypertensive cardiovascular disease**
021-US0191-1334	67/M	Naproxen 500 mg BID	47	Pulmonary embolus
087-US0021-0182	**56/M**	**Celecoxib 200 mg QD**	**30**	**Arteriosclerotic Cardiovascular disease**
Deaths After Drug D/C				
020-US0052-0683	62/F	Celecoxib 100 mg BID	26/ 54	Pulmonary carcinoma
020-US0033-0768	**80/F**	**Celecoxib 200 mg BID**	**6/45**	**MI**

a. Data from Integrated Safety Summary, Text Table 67. Table shows all deaths from controlled trials, including those that occurred after the study drug was discontinued. For those two subjects, the # of days after drug discontinuation for the death is shown after the day of death.

Ten deaths occurred during the long-term open-label study prior to the database cutoff date (November 21, 1997), and are summarized in table 54 below. The duration of treatment ranged from 15 to 273 days, with a final regimen of 200 mg BID for four patients, 300 mg BID for two patients and 400 mg BID for four patients. The subjects in bold letters (9/10, 90%) died of cardiovascular disease.

Table 54. Deaths in the Long-Term Trial Prior to NDA Cutoff Date[a]

Subject #	Age/ Sex	Treatment	Day of Death	Cause of Death
024-US0001-0010053	**65/F**	**Celecoxib**	**196**	**Myocardial rupture post-MI**

		400 mg BID		
024-US0023—0230020	**76/M**	**Celecoxib 200 mg BID**	**45**	**MI, cardiac failure**
024-US0024—0240004	**58/M**	**Celecoxib 400 mg BID**	**273**	**MI**
024-US0052—0520043	**83/F**	**Celecoxib 300 mg BID**	**193**	**Coronary thrombosis**
024-US0053—0530001	**80/M**	**Celecoxib 200 mg BID**	**159**	**Massive coronary**
024-US0058—0580018	**59/M**	**Celecoxib 200 mg BID**	**246**	**Ischemic heart disease**
024-US0066—0660004	60/M	Celecoxib 400 mg BID	155	Adenocarcinoma
024-US0073—0730060	**84/F**	**Celecoxib 400 mg BID**	**243**	**Respiratory failure, CHF**
024-US0121—1210052	**52/M**	**Celecoxib 300 mg BID**	**114**	**MI**
024-CA0139—139009	**57/F**	**Celecoxib 200 mg BID**	**15**	**Subarachnoid hemorrhage**

a. Data from Integrated Safety Summary, Text Table 66.

There were also five deaths in the long-term, open-label study between the database cutoff (November 21, 1997) date and May 1, 1998. These deaths are listed in table 55 below; all were due to cardiovascular disease (and are shown in bold letters).

Table 55. Deaths: Long-Term Open-Label Trial After NDA Cutoff [a].

Subject #	Age/ Sex	Treatment	Day of Death	Cause of Death
024-US0001-0010076	**74/M**	**Celecoxib 400 mg BID**	**336**	**Heart block**
024-US0024-0240024	**71/M**	**Celecoxib 400 mg BID**	**32**	**Coronary artery disorder**
024-US0073-0730189	**71/F**	**Celecoxib 400 mg BID**	**37**	**MI**
024-US0110-1100006	**61/F**	**Celecoxib 400 mg BID**	**471**	**MI**
024-US0116-1160042	**78/F**	**Celecoxib 200 mg BID**	**88**	**Aortic Aneurysm**

a. Data from Integrated Safety Summary, Text Table 67.

Finally, there were five deaths that occurred more than 28 days after the last dose in any study reported in this NDA (note that the two patients in the 020 trial are included in the table above) and are summarized in table 56. Two of these patients died after participation in trial 020 and three died following participation in Study 024. Of the five celecoxib subjects in this group, two died of cardiovascular disease (40%).

Table 56. Deaths That Occurred More than 28 Days After Last Dose[a].

Subject #	Age/Sex	Treatment	Day of Death	Days after Last Dose	Cause of Death
020-US0052-0683	62/F	**Celecoxib 100 mg BID**	26	54	Pulmonary carcinoma
020-US0033-0768	**80/F**	**Celecoxib 200 mg BID**	**6**	**45**	**MI**
024-US0027- 0270004	**66/M**	**Celecoxib 400 mg BID**	**334**		**Anterior MI**
024-CA0087-0870100	66/M	**Celecoxib 200 mg BID**	173	29	Sepsis, pneumonitis
024-US0042- 0420004	77/F	**Celecoxib**	111	36	Pulmonary carcinoma

		200 mg BID			

a. Data from Integrated Safety Summary, Text Tables 66 and 68.

Total Mortality

Depending on the population used for the denominator, mortality can be calculated in two ways using the information from the Cx database, summarized in table 57 and 58 below. The first way uses the number of subjects exposed to the drug in each treatment group, independent of the duration of that exposure (Table 57).

Table 57. Deaths per Patients Exposed in NDA 20-998[a].

Population	Number of Deaths	Number of Exposed Subjects	Crude Mortality Incidence
Controlled North American OA/RA Trials			
Deaths during Trial			
Placebo	0	1864	0%
Celecoxib	2	6376[e]	0.03%
Active Control	4	2768	0.14%
All known deaths[b]			
Placebo	0	1864	0%
Celecoxib	4	6376[e]	0.06%
Active Control	4	2768	0.14%
Long-term, Open-label Trial			
Deaths before cut-off date	10	5155	0.19%
Known deaths during celecoxib use	15[d]	5155	0.29%
All known deaths[c]	18	5155	0.35%

a. Data from Integrated Safety Summary, including Text Tables 65-68 and Summary table 2.9. Confirmed with the sponsor.
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.
c. For all patients who received celecoxib. 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 above).
d. Includes five deaths that occurred during celecoxib administration, reported after the cut-off date for the ongoing trial.
e. Number equals the total number of individual patients in the OA and RA trials (4151 and 2086, see earlier tables).

It is also fruitful to calculate mortality using the data on patient-years of exposure as the denominator as in the table 58 below.

Table 58. Mortality Rate: Deaths per Patient-Years of Exposure

Population	Number of Deaths	Patient-yrs of Exposure[e]	Mortality Rate
Controlled N.A. OA/RA Trials			
Deaths during Trial			
Placebo	0	208	0.00%
Celecoxib	2	1020	0.19%
Active Control	4	535	0.75%
All known deaths[b]			

Placebo	0	208	0.00%
Celecoxib	4	1020	0.39%
Active Control	4	535	0.74%
Long-term, Open-label Trial			
Deaths before cut-off date	10	2672	0.37%
Known deaths during celecoxib use	15[d]	4274	0.35%
All known Deaths[c]	18	4274	0.42%

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 Rate due to Cardiovascular (CV) Disease and for Total Mortality

As noted table 59 below, the crude rates of death due to CV disease in both the Cx and active control groups were higher than placebo:

Table 59. Cardiovascular Mortality Rates: North American Arthritis Trials[1]

	No. deaths	No. Exposed	Pt-years of Exposure	Mortality Incidence	Mortality Rate
Cardiac deaths in trial					
Placebo	**0**	**1864**	**208**	**0.00%**	**0.00%**
Celecoxib	**1**	**6376**	**1020**	**0.02%**	**0.10%**
Active control	**2**	**2768**	**535**	**0.07%**	**0.37%**
All known cardiac deaths[2]					
Placebo	**0**	**1864**	**208**	**0.00%**	**0.00%**
Celecoxib	**2**	**6376**	**1020**	**0.03%**	**0.20%**
Active control	**2**	**2768**	**535**	**0.07%**	**0.37%**

1. Data from Text Tables 65-65, ISS.
1. Includes one death in active control group and two deaths in the Cx group after trial completion. These deaths occurred >28 days after last dose of study medication.

It should be noted that these relationships between treatment groups and CV deaths when analyzed by Kaplan-Meier plots (see cardiorenal consult for more details).

Of interest, table 60 compares the rates of CV mortality in patients arranged according to highest dose of Cx received in the long-term trial.

Table 60. Cardiovascular Mortality Rates by Increasing Dose: Long-Term Trial[1,2]

Cx dose (BID)	No. deaths	Patient-years of exposure[4]	Crude Mortality Rate[3]
100 mg	**0**	**519**	**0%**
200 mg	**4**	**1271**	**0.31%**
300 mg	**2**	**340**	**0.59%**
400 mg	**3**	**465**	**0.64%**

1. Data from Text Tables 65-68, ISS.
2. Deaths occurred prior to cutoff of Nov. 21, 1997.
3. Mortality in deaths/pt-years (x100)

4. Data from Appendix Table 4.3, ISS.

Conclusions regarding deaths due to cardiovascular causes:
It appears that most of the deaths in both the controlled trials and the open-label extension are from CV causes. Combined with the apparent relationship with Cx dose (Table 60), this suggests that there is some association between Cx use and cardiovascular mortality. As has been noted elsewhere in this review, the lack of effect of Cx on platelets may help to explain these results compared to active control (probably not to placebo). However, the rates with Cx appear to be lower those seen with active controls (Table 59) suggesting this is not a good explanation.

It would appear that any adequate interpretation of these results is confounded by a number of factors. The population studied is generally older (with a substantial percentage of geriatric patients) with their associated increased CV risks factors (i.e. increased use of meds, more diabetes, hypertension, etc.). The number of events is small making adequate statistical conclusions difficult since a few deaths in the placebo group (for example) can dramatically change results. Also, in the long-term study of Cx, there are no control groups which forces reliance on the use of other large databases which may not properly mimic the subjects in these trials.

Therefore, it is not possible to conclude that use of Cx is associated with excess CV mortality. However, it is also not possible to rule it out. The "large and simple" trials currently underway looking at GI endpoints, along with post-marketing use should clarify this issue.

Conclusions Regarding Cx Safety:

The safety of Cx was addressed throughout NDA 20-998. This NDA represents not only a new molecular entity in Cx, it also would appear to represent the first compound with properties sufficient to distinguish itself as "selective" or "specific" for COX-2. Therefore, it is appreciated that a discussion of the safety of Cx may, or may not, represent a discussion regarding the theoretical advantages of COX-2 selective or specific. Only time, and more compounds of similar characteristics, will answer these questions.

Overall, and as a conclusion, Cx has demonstrated that it is a safe compound when given in the range of doses studied in the analgesic and arthritis trials of this NDA. Particular safety issues are summarized as follows:

1 Considering both the controlled North American and International arthritis trials, along with the placebo- and active control patients added to the long-term, safety trial, there were 8044 (4223 OA, 2098 RA, 1723 open-label) unique patients exposed to Cx at the time of the NDA database cutoff. By adding in the Phase 1 and Pain subjects, this number increases to 9574 patients/subjects to Cx at any dose. This number further increases to 10,704 patients/subjects by adding the new patients in the 120-Day Safety Update.

2 **Compared to placebo, Cx does not affect platelet function as demonstrated by *ex vivo* platelet aggregation to collagen or arachidonate and TxB_2 levels, even when given at supratherapeutic doses. Celecoxib also did not significantly increase bleeding times when compared to placebo; technical variability limits interpretation. Serum TxB_2 levels were not reduced by Cx to sufficiently enough affect platelet function. Adverse event and clinical laboratory data indicated that Cx use was not associated with hemorrhagic events related to platelet function. Thrombotic events, including MIs, occurred. Consequently, patients that require thromboprophylaxis may still require low dose aspirin or other antiplatelet agents.**

3 **The multiple studies convincingly show that Cx, used at the proposed dosages of 100 to 200 mg BID, was associated with a statistically significantly lower incidence of gastroduodenal ulcers and gastric erosions compared to naproxen 500 mg BID in all three pivotal studies. The one study comparing Cx 200 mg BID to ibuprofen 800 mg TID revealed robust support for the safety claims related to gastroduodenal lesions.**

4 **The data comparing Cx to diclofenac were inconclusive. Study 041 suggested endoscopic superiority over diclofenac but study 071 showed no significant differences. However, study 071 had a larger evaluable endoscopy cohort and ulcer-free baseline endoscopy giving a better picture of the *de novo* and drug related ulcer incidence. On the other hand, study 041 was a study of longer duration. The 4% ulcer incidence at 4 weeks and 7% final cumulative ulcer rate at 12 weeks in study 071 was within the range of ulcer rates on Cx in the other studies over 12-24 weeks.**

5 **None of the GI studies were designed to address the issue of comparability to placebo.**

6 **The lack of consistent association between H. pylori and ulcer incidence across all treatment was seen regardless of the methodology used to detect this infection.**

7 **When data from the five pivotal endoscopic studies are combined, there is a statistically significant ulcerogenic effect of low-dose aspirin in the Cx group. This aspirin enhanced rate, however, was still lower than the ulcer rate among the NSAID groups. There was no effect of aspirin in the active NSAID comparators when taken as a whole. Nonetheless, these trials were not designed to analyze the role of aspirin co-administration. The risk of ulceration of Cx and aspirin use, however, remains lower than the risk of gastroduodenal ulcers associated with the use of naproxen or ibuprofen.**

8 **Endoscopically-defined ulcers have been defined as the surrogate of choice in this NDA. Future studies need to address the true clinically meaningful endpoints to corroborate the assumption that the development or presence of endoscopic ulcers correlates with adverse clinical outcomes and to quantify this relationship, if possible. The lack of standardization of definitions and procedures is of concern for such future studies.**

9 **No measurements of acid-base balance (e.g. serum bicarbonate, arterial pH) performed as part of any trial in the NDA. Therefore, an adverse effect of Cx on acid-base balance cannot be excluded, particularly in the context of the observed increase in hyperchloremia.**

10 **Both Cx and comparator NSAIDs (in short-term trials) inhibited prostaglandin PGE_2 and 6-keto-PFG1 α excretion by the kidney to more or less the same extent. Both had significant inhibitory effects on the excretion of urinary prostaglandins when compared to placebo. Cx caused slightly less of a decrease in GFR in one study (010). Both Cx and naproxen inhibited serum renin and urinary (11-dehydro-TxB2) thromboxane levels.**

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11 There was an association between Cx administration and the development of clinically significant edema (especially peripheral edema), similar to comparator NSAIDs, and clearly distinguished from placebo. Both naproxen and Cx cause sodium retention. There was no statistically significant association between ≥1 kg weight gain and the occurrence of 'peripheral edema' in a subset of patients with edema as an AE, although a higher % of both the Cx and active control group patients had both.

12 There was an association between Cx administration and the development of worsened hypertension in susceptible individuals, again similar to NSAIDs, and clearly distinguished from placebo.

13 There is a definite association between Cx use and an increased incidence of hypophosphatemia, and hyperchloremia compared to placebo and similar to active controls. There was no increase in bony fractures in those individuals with these abnormalities, 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. The clinical consequences of these changes remain to be determined.

14 There was a trend towards an increase incidence of elevated serum creatinine values and elevated BUN with proteinuria in both the Cx and active control groups relative to placebo.

15 The laboratory surrogates for renal toxicity suggest, but do not confirm, a link between Cx use and clinically relevant nephrotoxicity similar to NSAIDs.

16 There is no evidence to suggest that Cx has unique renal toxicities not shared by NSAIDs, or evidence of a renal toxicity caused by NSAIDs that occurs at a significantly higher incidence rate with Cx.

17 The pattern of AEs reported in both the controlled and the long-term trials is similar to that expected for NSAIDs.

18 There were several individuals taking Cx who were withdrawn from the long-term trials because or renal AEs including acute renal failure, edema and worsened hypertension.

19 While there were no clear cut cases of Cx-induced renal failure requiring dialysis, it remains to be determined whether severe renal injury will occur at the same rate that is seen with NSAIDs.

20 The renal effects of Cx are clearly distinguished from placebo.

21 The NDA does not reveal a strong signal pointing towards substantial clinically serious renal disease (i.e. large numbers of patients with acute renal failure requiring dialysis, nephrotic syndrome, papillary necrosis, interstitial neprhritis). This will require a larger database.

22 The endocrine/metabolic safety profile of Cx is certainly no worse than the active controls.

23 Analysis of the data from the elderly population demonstrates that Cx is safe and well tolerated in the elderly, and poses no apparent additional safety considerations which do not apply to the younger age group.

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24 Myocardial infarction was noted to occur at a higher rate in Cx than placebo patients. In the long-term trial, the predominate (90%+) cause of death for patients taking Cx at any dose was cardiovascular. The majority of these deaths represented progression of previously known CV disease. There is no apparent relationship between any given duration of exposure to Cx and increased mortality. The administration of Cx cannot be linked to any rare or unusual cardiac toxicities based on the available data. The available data do suggest the effects of Cx are similar to NSAIDs with regard to the "cardiac" effects of hypertension and edema.

25 Rashes and related cutaneous reactions were among the more frequently noted AEs associated with Cx treatment. The rashes were generally mild in severity, and often associated with urticaria or pruritus. Rash was the single most common reason for withdrawal from study treatment. There was an increase in incidence of rash at higher Cx doses (maximal with the 400 mg BID dose) suggesting a dose-response relationship. Importantly, there were no serious cutaneous reactions associated with Cx treatment.

26 In view of the possible etiologic link to sulfonamide sensitivity, physicians should exercise caution in prescribing CX to patients with a known history of systemic sulfa reaction.

27 Respiratory events were common in all treatment groups and occurred at similar incidence, suggesting that the high frequency simply reflected the common nature of these disorders in the general population. Bronchitis and associated bronchospasm are not apparent to be exacerbated by celecoxib.

28 Review of the data regarding central and peripheral nervous system and psychiatric AEs does not reveal a pattern suggestive of deleterious effects from Cx use.

29 The available data does not suggest that Cx is associated with an increased risk of infection.

30 **The most frequent adverse events were headache, dyspepsia, upper respiratory tract infection, diarrhea, and nausea.**

31 **Events that were frequent in occurrence (>1%) and associated with significantly greater incidences or withdrawal rates for Cx than placebo included GI complaints, rashes or itching, peripheral edema, pharyngitis, and upper respiratory tract infection.**

32 The rate of withdrawal for adverse events for all doses of Cx appears better than comparators but NOT equivalent to placebo.

33 None of the serious adverse events that have occurred in NDA 20-998 appear to be obviously related to use of Cx.

34 No outstanding safety issues have been demonstrated during the clinical trials conducted to investigate the treatment of pain.

35 The data indicate that there was not an increased risk of neoplasms or malignancies for patients taking Cx.

36 None of the data suggest that Cx is associated with deleterious effects on the musculoskeletal system, including increases in the incidence of fractures.

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Overall Discussion/Conclusions Regarding Celecoxib:

It has been argued that Cx represents a compound that is "selective" or "specific" for COX-2. The exact definition of a COX-2 selective agent, and as to whether it is moderately or highly selective or specific has yet to be adequately addressed. Of note, the number of peer-reviewed articles on this topic is increasing and the WHO has recently declared Cx to be in a unique therapeutic class based upon its mechanism of action (MOA). Therefore, in this review, it could be asked how much are we testing the drug, the theory of the drug, or both?

Although the exposure to Cx in this NDA has been large, this is still a "NDA" look at the drug, not a post-marketing look. Many of the questions (regarding both safety and efficacy) that need to be answered, can not be adequately addressed until Cx has been in the market and accumulated the exposures with such marketing. For example, one of these issues includes what will happen with widespread exposure in patients who are not aware or adequately questioned about having allergies to sulfonamide-containing products. This is a universal problem of extrapolating results from clinical trials where patients are "included" or "excluded" from the experience in "all comers" once a compound is approved.

Regarding safety, many would argue that since non-selective NSAIDs also inhibit COX-2, any safety concerns from this perspective should already be obvious from the numerous compounds approved and widely used to date. Others would argue that we do not know the consequences of "long-term, high-grade" inhibition of COX-2 and what types of compensatory mechanisms may come into play in this situation. It must be noted that the distribution and molecular biology of COX-2 is rapidly evolving.

Therefore, when considering the safety of COX-2 agents from a MOA standpoint, it may really depend on the particular tissue/target and whether or not COX-2 is present, and under what conditions. For example, the safety of COX-2 agents would theoretically be different in a target such as platelets which are widely assumed not to have COX-2 (because they have no nuclear machinery to make an inducible enzyme); from the safety profile in an organ where COX-2 is present, such as the kidney. Intermediate between these "clear-cut" extremes would be a organ such as the stomach which may only have significant levels of COX-2 during a "diseased" state such as infection with Helicobacter pylori or during the healing phase of an ulcer's natural history.

It must also be noted here that, from a safety perspective, COX-2 agents may not behave like non-selective agents because of nature of the target, COX-2. In the early understanding of COX-2, drugs such as Cx were thought to target only an inducible enzyme. Even though it is now appreciated that COX-2 is expressed constitutively in some areas (like kidney, brain, pancreas), COX-2 (unlike COX-1) is inducible. This

would suggest that the body has a mechanism to overcome inhibition of COX-2, this does not appear to be the case with COX-1. That there may be such "upregulation" of COX-2 is suggested by the "dose-creep" phenomenon noted in the open-label, long-term trials with OA and RA (see below).

The following patient summary, taken from the 120-Day Safety Update represents many of the issues surrounding Cx and COX-2 agents:

> **Patient 024-US0130-1300010 was a 47-year-old female with a history of RA, sinusitis, tuberculosis, hysterectomy, osteoporosis, gastroduodenal ulcers, gastrointestinal bleeding, and gastrointestinal NSAID intolerance. Concomitant medications included azathioprine, methotrexate, prednisone, calcium, etidronate disodium, folic acid, and diphenhydramine hydrochloride. After successfully completing Study 022 in which the patient was randomized to celecoxib 100 mg BID, she was immediately entered into the long-term open label study and began taking celecoxib 200 mg BID. The dosage was increased to 300 mg BID 42 days later, and to 400 mg BID 67 days after that. Sixty-seven days after the last dose adjustment, the patient vomited two times, filling the commode with frank blood. She also complained of black, tarry stools and gnawing stomach pain after the episodes of hematemesis. She discontinued study medication on her own and started taking sucralfate on the same day. Vital signs were not recorded on that day, but the patient saw her private physician two days later. At that time, blood pressure was 94/60 mmHg, pulse was 76 bpm, and temperature was 97.8°F. An endoscopy was performed that same day, which revealed gastric and esophageal ulcers. The patient was continued on sucralfate and started on omeprazole. The patient did not resume celecoxib treatment and was terminated early from the study. Laboratory results taken the day after endoscopy were hemoglobin 10.1 g/dL, hematocrit 31.0% (decreased from a Baseline hematocrit of 40.0%; she also tested positive for H. pylori antibody by FlexSure test). The patient has recovered. The Investigator felt this event was related to study**

Clearly, this patient developed a "clinically relevant" UGI event and she was in a risk group to have such an event. It could be argued that she was at a greater risk because she increased her dose of Cx, but she increased this dose for a reason, apparently she and her physician felt she needed it.

While most (≈70%) patients with OA or RA in the open-label, long-term studies increased their dose of Cx, most did not an event similar to this patient. This "dose creep" is recognized to occur with other drugs, including NSAIDs. It could be argued that this creep seems to occur for both the "analgesic" and "anti-inflammatory" doses of Cx since it did occur in patients with both OA and RA. However, the end doses appear higher in patients with RA vs. patients with OA; the latter is considered to have less of an inflammatory component than RA.

In conclusion, Celebrex had demonstrated that is generally safe and effective for treating the signs and symptoms of OA and RA. Trials for analgesia were not adequate enough to conclude that Celebrex is an analgesic but this is expected with ongoing trials. Similarly, the clinical significance of the lower rates of endoscopic

ulcers associated with Celebrex has yet to be established. In organs where COX-2 is present, such as the kidney, Celebrex looks more like a traditional NSAID. On the other hand, in targets where COX-2 is absent (such as platelets), Celebrex looks more like placebo. Overall, Celebrex is comparable to (or better than) active control NSAIDs while tending to be worse than (or, at times, comparable to) placebo.

Appendices

Deaths in NDA 20-998

Reviewer's comment: The following section is from the Appendix of the Cardiorenal Review

Deaths in the Celecoxib NDA Database

9.1.1 Deaths in patients who enrolled in a controlled arthritis trial
A total of eight subjects who enrolled in controlled arthritis trials died. Five deaths occurred during controlled arthritis studies, and three following discontinuation of study drug. The narratives for those subjects who died while receiving study drug are in the first section below. The narratives for the subjects who died after discontinuation of study drug are found in section 9.1.2 below.

Five of the individuals in the controlled arthritis group who died received celecoxib, while three received active control drug.

Table 9.1.1.1 Deaths during controlled trials in the NDA 20-998 database[a].

Subject #	Age/ Sex	Treatment	Day of Death	Cause of Death
Deaths During Study Drug Administration				
041-BE0002-0010	70/M	Celecoxib 200mg BID	81	Gallbladder carcinoma with liver metastasis
062-US0117-46761235	68/M	Naproxen 500mg BID	63	Brain-stem infarct
071-US0382-65811310	78/M	Ibuprofen 800mg TID	29	Obstructive pulmonary disease
071-US0333-46521451	53/F	Diclofenac 75 mg BID	1	Hypertension CV disease
087-US0021-0182	56/M	Celecoxib 200mg QD	30	Arteriosclerotic cardiovascular disease
Deaths After Drug D/C				
020-US0052-0683	62/F	Celecoxib 100mg BID	26/ 54	Pulmonary carcinoma
020-US0033-0768	80/F	Celecoxib	6/ 45	MI

021-US0191-1334	67/M	200mg BID Naproxen 500mgBID	47/ NA	Pulmonary embolus

a. Data from Integrated Safety Summary, Text Table 67. Table shows all deaths from controlled trials, including those that occurred after the study drug was discontintued. For those three subjects, the # of days after drug discontinuation for the death is shown after the day of death.

1. Patient No. BE0002-0010 (Carcinoma–Gallbladder to Liver) was a 70 year old male with a past history including cardiomyopathy, pulmonary hypertension, COPD, hyperthyroidism, cholelithiasis, hypercholesterolemia, hypergammaglobulinemia, and an enlarged liver was admitted to study and randomized to the celecoxib 200 mg BID treatment group. Patient began taking study medication on 5 February 1997. Seventy nine days after the start of dosing on 26 April 1997 the patient stopped taking study medication because of nausea. On 11 May 1997 he saw his general practitioner because of sudden nausea, vomiting and intermittent diffuse abdominal pain. The patient was hospitalized on for further investigation. His bilirubin and liver enzymes were elevated. He was found to have carcinoma of the gallbladder with metastases to the liver. He also had mild macrocytic anemia with no evidence of bleeding. Laboratory work included:

Hgb 10.3, Hct 31, WBC and Diff Normal, during hospitalization ECHO and CT , alpha-fetoprotein (0-12) 38, CEA (0-3) >90, Total Bilirubin 4.5, Indirect Bilirubin 2.7, SGOT 230, SGPT 111, LDH 4257, Alk Phos 360, and Gamma GT 442. The patient died on due to the carcinoma. No autopsy was performed.

2. Patient No. US0117-46761235 (Cerebrovascular Disorder) was a 68 year old male with a history of tonsillectomy, bilateral otitis externa, herpes zoster, post-herpatic neuralgia, arteriosclerotic cardiovascular disease, bilateral claudication, hypertension, removal of abdominal aortic aneurism, appendectomy, hemorrhoidectomy, right great toe fracture, mild scoliosis, hypercholesterolemia, and OA. The patient was enrolled into the study on 14 July 1997 and randomized to receive naproxen 500 mg BID. After 63 days of treatment, the patient could not get out of bed. He had right-sided weakness and felt he would fall if he tried to stand. He felt “very funny” and had blurred vision and slurred speech. He was taken to the emergency room where his blood pressure was elevated at 192/90. Central nervous system examination revealed slurred speech, blurred vision, mild vertical nystagmus, and abnormal right upper extremity finger-to-nose. Other physical examination was normal. Initial lab data was unremarkable. A CT scan of the head did not reveal any acute hemorrhage. Chest x-ray revealed mild cardiomegaly. Brain stem evoked potential was suggestive of acute brain stem infarct. The patient was admitted to the hospital and intravenous enalapril maleate was initiated. He was also treated with metoprolol tartrate and sublingual nifedipine. His speech and coordination improved somewhat the following day, but later that day he developed focal seizures and became unresponsive. He was treated with intravenous diazepam and phenytoin but remained unresponsive. His blood pressure was 167/90 and it was felt that he had probably had an extension of his initial brain stem cerebrovascular accident. He was intubated and was started on intravenous antibiotics. Blood cultures were negative. The patient died four days later. No autopsy was performed. Concomitant medications included quinapril, metoprolol succinate SR, doxepin, and atrovastatin.

3. Patient No. US0382-65811310 (Sudden Death) was a 78 year old male with a history of osteoarthritis, hearing loss, sinus congestion, hypertension and emphysema. The patient was enrolled into the study on 8 September 1997 and randomized to receive ibuprofen 800 mg TID. After 35 days of treatment, the patient experienced edema in his ankles and was withdrawn from the study. This subsided an unknown number of days after stopping study medication. Twenty four days later, the patient experienced severe abdominal pain. While getting into his car to go to the doctor, he collapsed and expired. The patient had previously been diagnosed with a urinary tract infection and was being treated by his primary physician. No autopsy was performed. Concomitant medications at the Early Termination Visit included nifedipine, metaproterenol sulfate and triamcinolone acetonide.

4. Patient No. US0333-46521451 (Arteriosclerosis) was a 53 year old female with a history of hypertension, hysterectomy, allergy to codeine, and osteoarthritis. The patient was enrolled into the study

on 25 August 1997 and randomized to receive diclofenac 75 mg BID. On , the patient was found dead at home by her daughter. Since the patient's family never returned the study medication containers, compliance or length of study medication cannot be determined. Her daughter stated the patient had " probably been dead for about one hour" when she was found. She also stated that the coroner's report listed the cause of death as "hypertensive cardiovascular disease." Concomitant medications included fluoxetine hydrochloride, buspirone hydrochloride, and losartan potassium.

5. Patient No. US0021-0182 (Coronary artery disorder) was a 56 year old male with a history of seasonal allergies, corrective lenses, presbyopia, asthma, benign inflamed lymph node in the groin area, diabetes mellitus type II, obesity, allergies to dust, mold, grass and cat hair, and osteoarthritis. The patient was enrolled into the study on February 9, 1998, and randomized to celecoxib 200 mg QD. After twenty-nine days of treatment, the patient was out of town at a basketball game and collapsed and due to arteriosclerotic cardiovascular disease while getting into his car. Concomitant medications included regular insulin, NPH insulin, metformin hydrochloride, epinepherine, albuterol, beclomethasone dipropionate, albuterol sulfate, and multivitamins. Study medication was continued up until the time of death.

9.1.2 Deaths during the Open-Label Uncontrolled, Long-term Administration of Celecoxib

Ten deaths occurred during the long-term open-label study prior to the database cutoff date (November 21, 1997), and are summarized below. The duration of treatment ranged from 15 to 273 days, with a final regimen of 200 mg BID for four patients, 300 mg BID for two patients and 400 mg BID for four patients.

Table 9.1.2.1 Deaths During the Long-Term Open Label Trial Prior to Database Cutoff Date of November 21, 1997[a].

Subject #	Age/ Sex	Treatment	Day of Death	Cause of Death
024-US0001-0010053	65/F	Celecoxib 400 mg BID	196	Natural causes
024-US0023--0230020	76/M	Celecoxib 200 mg BID	45	MI, cardiac failure
024-US0024--0240004	58/M	Celecoxib 400 mg BID	273	MI
024-US0052--0520043	83/F	Celecoxib 300 mg BID	193	Coronary thrombosis
024-US0053--0530001	80/M	Celecoxib 200 mg BID	159	Massive coronary
024-US0058--0580018	59/M	Celecoxib 200 mg BID	246	Ischemic heart disease
024-US0066--0660004	60/M	Celecoxib 400 mg BID	155	Adenocarcinoma
024-US0073--0730060	84/F	Celecoxib 400 mg	243	Respiratory failure, CHF

024-US0121--1210052	**52/M**	**BID Celecoxib 300 mg BID**	**114**	**MI**
024-CA0139--139009	**57/F**	**Celecoxib 200 mg BID**	**15**	**Subarachnoid hemorrhage**

a. Data from Integrated Safety Summary, Text Table 66.

There were also five deaths in the long-term open label study between the database cutoff date and May 1, 1998. Their narratives are included below.

Table 9.1.2.2Deaths During the Long-Term Open Label Trial After Database Cutoff Date of November 21, 1997[a].

Subject #	Age/ Sex	Treatment	Day of Death	Cause of Death
024-US0001-0010076	**74/M**	**Celecoxib 400 mg BID**	**336**	**Heart block**
024-US0024-0240024	**71/M**	**Celecoxib 400 mg BID**	**32**	**Coronary artery disorder**
024-US0073-0730189	**71/F**	**Celecoxib 400 mg BID**	**37**	**MI**
024-US0110-1100006	**61/F**	**Celecoxib400 mg BID**	**471**	**MI**
024-US0116-1160042	**78/F**	**Celecoxib 200 mg BID**	**88**	**Aneurysm**

a. Data from Integrated Safety Summary, Text Table 67.

Finally, there were six deaths that occurred more than 28 days after last dose in any study reported in this New Drug Application. Two of these patients died after participation in trial 020, one died after participation in Study 021, and three died following participation in Study 024. The narratives for these subjects are also included below.

Table 9.1.3 Deaths That Occurred More than 28 Days After Last Dose[a].

Subject #	Age/ Sex	Treatment	Day of Death	Days after Last Dose	Cause of Death
020-US0052-0683	62/F	Celecoxib 100 mg BID	26	54	Pulmonary carcinoma
020-US0033-0768	80/F	Celecoxib 200 mg BID	6	45	MI
021-US0191-1334	67/M	Naproxen 500 mg BID	47		Pulmonary embolus
024-US0027-0270004	65/M	Celecoxib 400 mg BID	334		Anterior MI
024-CA0087-0870100	66/M -	Celecoxib 200 mg BID	173	29	Sepsis, pneumonitis
CL004 024-US0042-	77/F	Celecoxib	111	36	Pulmonary

a. Data from Integrated Safety Summary, Text Tables 66 and 68.

1. Patient No. US0033-0768 (Myocardial Infarction) was an 80-year-old female with a history of OA, hypertension, borderline diet-controlled diabetes, hysterectomy, appendectomy, cholecystectomy, lumbar laminectomy, anterior cervical decompression and fusion, cataract surgery and rectal surgery for

fistulas. The patient was enrolled into the study on 18 October 1996 and randomized to receive celecoxib 200 mg BID. After five days on treatment, the patient experienced severe chest pain lasting three hours which was associated with vomiting, diaphoresis and shortness of breath. She was hospitalized for an inferior wall myocardial infarction. It was noted that the patient had experienced intermittent chest pain for three days prior to hospital admission and had complained of anginal symptoms which occurred both with activity and at rest for six months prior to enrollment into the study. Treatment included aspirin, tissue plasminogen activator or a novel plasminogen activator under investigation. Additional treatment included morphine, intravenous heparin, intravenous nitroglycerin, ticlopidine and metoprolol. An ECG demonstrated ST fullness in the inferior leads with T-wave inversion and ST elevation with right-side ECG in V4-V6. A chest x-ray showed cardiomegaly and an atherosclerotic aorta with no other acute abnormalities. Emergency left heart catheterization was performed showing 100% occlusion of the mid-right coronary artery. Percutaneous transluminal coronary angioplasty was performed with suboptimum blood flow; therefore, a coronary stent was deployed which was successful. Concomitant medication included triamterene/hydrochlorothiazide, diphenoxylate/atropine and alprazolam. Study medication was discontinued and the patient was terminated early from the study. The patient was discharged from the hospital and reported feeling well. The patient was unable to schedule the Early Termination visit. Forty-five days following onset of the event, the patient expired in her sleep. No autopsy was performed. The death certificate listed immediate cause of death probable myocardial infarction due to coronary artery disease and congestive heart failure.

2. Patient No. US0052-0683 (Pulmonary Carcinoma) was a 62-year-old female with a history of tobacco use, no taste or smell, hysterectomy, pneumonia, hypertension, arthroscopy, fibromyalgia, degenerative disc disease and OA. The patient was enrolled into the study on 19 September 1996 and randomized to receive celecoxib 100 mg BID. Eight days after treatment began, the patient was referred to a pulmonologist for increased dyspnea. Chest x-ray revealed a right upper lung nodular density. On Study Day 12, a CT scan of the patient's chest showed a 2.2 cm spiculated right upper lobe mass, consistent with a carcinoma. Bronchoscopy was performed thirteen days later and bronchoalveolar lavage cytology report showed atypical cells that were non-diagnostic. Study medication was discontinued at this time and the patient was withdrawn from the study. Thirty-four days later the patient was admitted for a right upper lobe lung mass. A thoracotomy with right upper and middle lobectomy was performed. No evidence of metastatic disease was found. The patient developed post-operative atelectasis with possible pneumonia three days later which advanced to adult respiratory distress syndrome (origin unknown) ending in death sixteen days after onset. No autopsy was performed. Other concomitant medications included nifedipine, fluoxetine, estradiol, cephalexin and minocycline.

3. Patient No. US0191-1334 (Gallbladder Disorder, Death from Myocardial Infarction or Massive Pulmonary Embolism) was a 68 year old male with a history of OA, deep venous thrombosis following a tractor accident and pulmonary emboli. The patient has previously participated in celecoxib clinical trial #N49-96-02-047 for three days. One hundred and thirty four days later after Early Termination from this study due to treatment failure, the patient was enrolled into the current study (3 June 1997) and randomized to receive naproxen 500 mg BID. After forty six days of treatment the patient was on an out-of-town trip when he began experiencing heartburn. The heartburn progressed and became severe and was accompanied by nausea and vomiting. After returning home, he was hospitalized the following day. Physical examination revealed abdominal tenderness. He had an elevated white blood cell count. An electrocardiogram revealed some changes, including left bundle branch block, but the patient was cleared for surgery by cardiology consult who felt there were no acute changes or evidence of acute myocardial injury. Laparoscopic cholecystectomy was initially attempted but because of severe gangrenous and inflammatory changes in and around the gallbladder, it was necessary to do an open cholecystectomy. An operative cholangiogram was within normal limits. The gallbladder was found to have sludge and stones with a stone impacted in the neck of the gallbladder along with a possible common bile duct stone. The patient was maintained on intravenous fluids, intravenous antibiotics, and subcutaneous heparin postoperatively. The patient was unable to tolerate oral feedings and five days after surgery nausea and vomiting increased. An ultrasound of the abdomen showed a suspected fluid collection in the right upper quadrant. CT scan showed a large periduodenal hematoma. The patient's white blood cell count and amylase were elevated and some degree of pancreatitis was also suspected. A central line was placed, the patient was started on total parenteral nutrition and anticoagulant therapy was discontinued. The patient

then developed some hallucinations and erratic behavior and bizarre complaints, and eight days after surgery, apparently suffered a cardiopulmonary arrest. The patient was resuscitated and was transferred to intensive care. His ECG at that time showed tachycardia with left bundle branch block. Shortly after transfer to the unit, he developed an idioventricular rhythm and was pulseless. Resuscitation attempts were unsuccessful and the patient was pronounced dead. It was the opinion of the cardiologist who attended the event that he had either suffered a massive myocardial infarction or massive pulmonary embolus. An autopsy was not done. No other concomitant medications were being taken. Study medication was interrupted during hospitalization.

4. Patient No. US0001-0053 (Death) was a 66 year old female with a history of cataracts, appendectomy, hemorrhoidectomy, postmenopause, fibrocystic breast disease, bilateral mastectomy, bilateral breast implant, squamous cell carcinoma, iron deficient anemia, multiple drug allergies, and RA. The patient had previously participated in the N49-96-02-022 clinical trial during which she had received placebo. After successfully completing this study, she was entered into the long-term safety study and began taking celecoxib 200 mg BID on 25 February 1997. Dosage was increased to 300 mg BID 42 days later on 8 April 1997. Nine days after that on , the patient had a basal cell carcinoma removed from the right side of her nose. One hundred and thirty three days later (on 28 August 1997), dosage was increased to 400 mg BID. Approximately 12 days later, on or about , the patient died of "natural causes." Concomitant medications included prednisone, methotrexate sodium, folic acid, and ferrous sulfate.

5. Patient No. US0001-0076 (Heart Block, Hypoglycemia,Hyperglycemia) was a 74 year old male with a history of seasonal allergies, pericarditis,prostate surgery for benign prostatic hypertrophy, bilateral ankle fusion, psoriasis, snoring, hypertension, chronic obstructive pulmonary disease, and rheumatoid arthritis. The patient previously participated in celecoxibclinical trial #N49-96-02-022, during which the patient had received either placebo, celecoxib 100 mg BID, 200 mg BID, 400mg BID or naproxen 500 mg BID. After being withdrawn early due to treatment failure, he was entered into the long-term safety study, N49-96-02-024, and began taking SC-58635200 mg BID on April 23, 1997. Dosage was adjusted to 300 mg BID 5 days later, on April 28, 1997 and to 400 mg BID 4 days later, on May 2, 1997. Three hundred and twenty-seven days later, on , the patient was wheeled into the doctor's office and was cyanotic and lethargic. The patient was incubated and taken to the emergency room where he was pronounced dead. The patient was diagnosed as being in total heart block, hypoglycemic (blood sugar of 16), and hyperkalemic (potassium was 9.0). Amphetamines and antidepressants were detected in the patient's urine. The patient had gone to see his primary care physician one day prior to this event, on , and the physician said the patient was "OK". Concomitant medications included prednisone, pencillamine, trinallin and amlodipine. The date of last dose is unknown at this time.

6. Patient No. US0023-0020 (Myocardial Infarction, Cardiac Failure) was a 76 year old male with a history of appendectomy, testicle cyst (removed), malaria, diabetes, sinusitis, insomnia, fractures of foot, shoulder and nose, hyperlipidemia, hypertension and RA. The patient had previously participated in the N49-96-02-023 clinical trial during which he had received naproxen 500 mg BID. After terminating early from this study due to treatment failure, the patient entered into the long term safety study and began taking celecoxib200 mg BID on 1 April 1997. After 23 days of treatment, on , the patient was hospitalized for a previously scheduled total hip replacement. After 39 days of treatment, on , the patient was hospitalized for a right deep venous thrombosis. Seven days after discharge, on , the patient was seen in the emergency room for constant anterior chest pain, which had began approximately two days earlier and was not associated with radiation, diaphoresis,or dyspnea. The patient was then hospitalized the following day, on , with a myocardial infarction of the anterior wall. Treatment included intravenous nitroglycerin and heparin sodium, oxygen, and monitoring and evaluation of cardiac status. Lab work revealed glucose of 227 and CK of 52. Repeat CKs were 456, 784, and 687 with MBs of 82.6, 150.1, and 121.7. Ventilation-perfusion lung scan performed due to an episode of shortness of breath showed a low probability of a pulmonary embolus. Portable chest x-ray showed no acute cardiopulmonary disease. Echocardiogram showed normal left ventricular contractility, ejection fraction of approximately 52%, normal intracardiac chambers, and normal valvular function. Cardiac catheterization performed six days later, on , showed coronary artery disease with 20% left main proximal stenosis, 100% left circumflex distal stenosis, left anterior descending with someplaquing in the midportion but no focal stenosis more than 50%, 90% mid right coronary artery stenosis, and left

ventricular ejection fraction of 50-55%. The patient was then transferred to another hospital that same day, where he underwent a percutaneous transluminal coronary angioplasty with stenting of the right coronary artery. Nine days after transfer and approximately one week after discharge, on , the patient developed a sudden onset of chest pain which was not relieved by three sublingual nitroglycerin. The patient was taken to the emergency room and was intubated and cardioverted after experiencing sustained ventricular tachycardia, ventricular fibrillation, and cardiac arrest. The patient was then admitted for an acute inferior wall myocardial infarction probably due to acute closure of the right coronary stent placed two weeks prior to admission, complicated by cardiogenic shock, hypotension with systolic blood pressure 60-70, and bradycardia with heart rate in the 30's. Electrocardiogram confirmed an acute inferior infarct showing acute ST segment elevation, severe bradycardia, and third degree heart block. Despite being on warfarin sodium, his protime was only 15 and INR was 1.3. Treatment included a temporary pacemaker as well as intravenous fluids, oxygen, morphine sulfate, Levophed, thrombolytic therapy, heparin sodium, and dopamine hydrochloride. The patient expired the following day, on , due to cardiogenic shock and acute myocardial infarction after an unsuccessful resuscitation attempt for pulseless ventricular fibrillation. Other concomitant medications included Centrum, multivitamins, metformin hydrochloride and nisoldipine.

7. Patient No. US0024-0024 (Coronary Artery Disorder) was a 71 year old male with a history of hypertension, myocardial infraction, peripheral bilateral edema due to cardiovascular disease, removal of ganglion cyst on left elbow, dentures, not-fasting hyperglycemia, hypercholesterolmia, hypertriglycaridemia, hypocalcemia, macular degeneration of right eye, right inguinal hernia repair, urinary tract infection, and rheumatoid arthritis. The patient had previously participated in celecoxib clinical trial #N49-96-02-023, during which the patient had received celecoxib 100 mg BID, 200 mgBID, 400 mg BID, naproxen 500 mg or placebo BID. After the patient successfully completed this study, he was entered into the long-term safety study and began taking celecoxib 200 mg BID on February 6, 1997. Dosage was adjusted to 300 mg BID 42 days later, on March 20 1997, and again adjusted to 400 mg BID 49 days later, on May 8,1997. Three hundred six days after last dose adjustment, on , the patient expired in his home due to cardiopulmonary arrest as a consequence of coronary artery disease. Concomitant medications included methotrexate sodium, multivitamin, folic acid, diltiazem hydrochloride, inadapamide, mononitrate, and baby aspirin. Study medication was continued until the time of death.

8. Patient No. US0024-0004 (Myocardial Infarction) was a 59 year old male with a history of cardiomegaly, lumbar and cervical spine surgery, umbilical hernia repair, peripheral edema, hypertension, hip replacement, spinal stenosis, muscle spasm, elevated creatine phosphokinase, two pack per day smoker, obesity and RA. The patient had previously participated in the N49-96-02-012 clinical trial during which he received celecoxib 400 mg BID for four weeks. One hundred and forty days after successfully completing this study, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID on 31 July 1996. Dosage was increased to 300 mg BID 42 days later, on 11 September 1996, and to 400 mg BID 21 days later on 2 October 1996. Two hundred and nine days after the last adjustment, on , the patient suddenly collapsed while at a horse race track. Following an unsuccessful resuscitation attempt, the patient was subsequently pronounced dead in the emergencyroom as a result of an acute myocardial infarction due to hypertensive heart disease. Examination on the body after death revealed distinguishable earlobe creasing and edema to the ankles. There was no indication of injury. No autopsy was performed.Concomitant medications included aurothioglucose, prednisone and lisinopril. (The Searle Medical Monitor elected to code this event as “sudden death” until more information about the evidence of M.I. was available).

9. Patient No. US0027-0004 (Anterior Myocardial Infarction) was a 66year old male with a history of tinnitus, hypertension, benign prostatic hypertrophy, mechanical low back pain, Baker’s cyst, right knee arthrotomy, lipoma of the right shoulder, cholelithiasis, exogenous obesity, anemia, choroidal nevus, and RA. The patient had previously participated in the N49-96-02-012 clinical trial during which he had received placebo. After successfully completing this study, he was entered the long-term safety study and began taking celecoxib 200 mg BID on 18 July 1996. Dosage was increased to 300 mg BID thirteen days later on 31 July 1996, and again increased to 400 mg BID twenty eight days later on 28 August 1996. Two hundred and eighty five days after the last adjustment on , the patient developed chest pressure while at rest with associated diaphoresis that persisted for one hour. He went to the emergency room where an electrocardiogram was negative. Treatment included sublingual nitroglycerin and nitroglycerin paste

with relief of his pain. Subsequent electrocardiogram revealed possible non-specific anterolateral T wave change and he was admitted for further evaluation on . On admission, his blood pressure was120/80 and pulse was 76 with no abnormalities noted on physical examination. A cardiac catheterization performed that same day revealed significant disease of the left anterior descending coronary artery, 90% discrete stenosis, followed by a large first diagonal that had a 75% stenosis (apical stenosis 70%). Left ventriculography revealed moderately severe anterolateral hypokinesis with an ejection fraction around 45 to 50% overall. One day later on , the patient underwent a percutaneous transluminal coronary angioplasty with implantation of a JR II intracoronary stent in the first diagonal and a J & J intracoronary stent in the left anterior descending. There were no residual stenoses. Post procedure, when his sheath was pulled, he developed some sinus bradycardia and associated hypotension, which was treated with no further sequelae. The patient had no further complaints of chest pain or shortness of breath and was discharged two days later on . Treatment included ticlopidine, acetylsalicylic acid, atenolol, andranitidine. Study medication was discontinued, and the patient was terminated early from the study on 17 June 1997 due to taking the above medications. The patient was started on diclofenac that same day. On the night of (sixty-three days later after terminating from the study) the patient developed chest pressure. This persisted and he went to the emergency room early the following morning on . Electrocardiogram showed acute anterior ST elevation. He was treated with thrombolytics. The chest pain continued and he was subsequently transferred to another hospital for further cardiac evaluation. On admission, lung sounds were diminished and heart rate and rhythm were regular with S1, S2, and S4 gallop. Peak creatine phosphokinase was 6581 with an MB of greater than 300. Potassium was 2.2, which was corrected to 4.5. Magnesium was 1.5. Following admission the patient underwent an emergency left heart catheterization with coronary angiography due to continued chest pain. This showed hazy proximal left anterior descending with subtotal occlusion of diagonal and thrombus in the distal left anterior descending. The patient was started on abciximab and an intra-aortic balloon pump was then inserted. He developed a wide complete tachycardia requiring intubation and subsequent CPR. The patient was resuscitated. In the cath lab the patient vomited approximately 200 cc of bright red blood and a gastroenterology consult was obtained. An acute GI hemorrhage was suspected either due to a Mallory-Weiss tear versus diclofenac induced surgery. It was also felt that anticoagulant therapy had contributed to the blood loss. Neurologically, the patient did not arouse post-code and developed mild clonic activity. On consultation, the neurologist felt that symptoms were indicative of a moderate to severe intracranial hypoxic event. The patient did not regain consciousness. He died the following day on . Concomitant medications included folic acid, methotrexate, hydroxychloroquine, and verapamil.

10. Patient No. US0042-0004 (Pulmonary Carcinoma) was a 77 year old female with a history of cardiomegaly, periodontal disease, hearing loss, hemorrhoids, breast cyst, myopia, chronic obstructive lung disease, smoker, pneumonia, shortness of breath and osteoarthritis. The patient had previously participated in celecoxibclinical trial #N49-96-02-022, during which she had received either placebo, celecoxib 50 mg BID, 100 mg BID, 200 mg BID or naproxen 500 mg BID. After successfully completing this study, she immediately entered into the long-term safety study and began taking celecoxib 100 mg BID on November 19, 1996. Dosage was adjusted to 200 mg BID 168 days later, on May 6, 1997. After another 288 days of treatment, on February 18, 1998, she was seen for her month 15 visit with complaints of increased shortness of breath and cough. She had completed a regimen of cefprozil on this same date. Chest x-ray was performed and showed a large infiltrate mass in the left lung. Computed tomography performed 5 days later, on confirmed alarge left hilar mass which appeared to have mediastinal invasion. Nine days later, on , a diagnostic bronchoscopy with endobronchial biopsy was performed and was suggestive of a bronchogenic neoplasm with secondary atelectasis. Pathology report of the left upper lobe bronchial biopsies showed non small cell carcinoma (possible large cell undifferentiated carcinoma) of the left upper lobe of her lung. Study medication was discontinued on March 10, 1998, and the patient was withdrawn from the study on March 12, 1998. Twelve days later, on , the patient was admitted for an exudative pleural effusion and a new onset of atrial fibrillation. She was treated with insertion of a chest tube and warfarin sodium. She was subsequently discharged on . Eleven days later, on , the patient was readmitted withincreasing shortness of breath. She was noted to have complete white out of her left lung. A chest tube was inserted, and 2 liters of fluid were removed. Other treatment included pain medication, antibiotics, steroids, breathing treatments, a radiation substantially, and she expired 4 days

later, on . Concomitant medications included triamcinolone acetonide, albuterol and calcium carbonate.

11. Patient No. US0052-0043 (Coronary Thrombosis) was an 84 year old female with a history of hypertension, coronary artery disease, cigarette smoking, occasional indigestion, atherosclerosis, hyperlipidemia, adult onset diabetes mellitus, anxiety attack, bronchitis, depression, and RA. The patient had previously participated in the N49-96-02-023 clinical trial during which she received celecoxib 400 mg BID. After being withdrawn early from this study due to a nosebleed, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID on 10 April 1997. Dosage was increased to 300 mg BID 14 days later, on 24 April 1997. One hundred and seventy nine days later, on , the patient died of a coronary thrombosis; a contributing cause of death was considered to be chronic obstructive pulmonary disease. Concomitant medications included alprazolam, ipratropium, albuterol, salmeterol xinafoate, vitamin E, baby aspirin, glipizide, Triavil, pentoxifylline, enalapril maleate, and lovastatin. The Investigator was uncertain of the association of the event with the study drug.

12. Patient No. US0053-0001 (Ventricular Fibrillation, Myocardial Infarction, Coronary Artery Disease) was an 80 year old male with a history of cataracts, spinal stenosis, cardiomyopathy, cardiac arrhythmia, angina, mild congestive heart failure, pneumonia, colon polyps, irritable bowel syndrome, constipation, hyperlipidemia, gastroduodenal ulcer, benign prostatic hypertrophy, meniscectomy, hypothyroidism, gout, hypertension, depression and OA. The patient had previously participated in the N49-96-02-020 clinical trial during which he received celecoxib 100 mg BID. After withdrawing early from this study due to treatment failure, the patient was entered into the long-term safety study and began taking celecoxib 100 mg BID on 11 September 1996. Dosage was increased to 200 mg BID 14 days later, on 25 September 1996. One hundred and thirty days later, on , the patient woke up " not feeling well". After eating breakfast, the patient left the table, collapsed and died. Death certificate reveals cause of death to be cardiorespiratory arrest due to ventricular fibrillation, acute myocardial infarction and coronary artery disease. Concomitant medications included methylcellulose, levothyroxine, allopurinol, propoxyphene, gemfibrozil, furosemide, digoxin, diltiazem, potassium chloride, losartan, sertraline and psyllium.

13. Patient No. US0058-0018 (Coronary Artery Disorder) was a 60 year old female with a history of allergic rhinitis, nasal congestion, refraction disorder, bilateral middle finger numbness, asthma, hemorrhoids, stress incontinence, cystocele,total abdominal hysterectomy and bilateral salpingo-oophorectomy, post-menopausal, intermittent back pain, right great toe fracture, lumbar laminectomy, bilateral calcaneal spurs, intermittent eczema, hypercholesterolemia, exogenous obesity, allergies to adhesive tape and amoxicillin, inhalant allergies, and OA. The patient had previously participated in the N49-96-02-021 clinical trial during which she received celecoxib mg BID. After successfully completing this study, the patient was entered into the long-term safety study and began taking celecoxib 100 mg BID on 20 February 1997. Dosage was increased to 200 mg BID 14 days later on 6 March 1997. One hundred and forty six days later, on the patient was found dead by her son. An autopsy performed one day later, on 31 July 1997, revealed arteriosclerotic cardiovascular disease with severe narrowing of the left anterior descending coronary, right coronary artery by atherosclerosis, and severe atherosclerosis of the aorta. No evidence of a recent or old myocardial infarction was noted. Hashimoto's thyroiditis and cholesterolosis of the gallbladder were also seen on autopsy. The death certificate shows the patient died of ischemic heart disease. Concomitant medications included Naldecon, pravastatin, estrogen, calcium carbonate, and allergy injection.

14. Patient No. US0066-0004 (Respiratory Insufficiency, Pulmonary Carcinoma, Treatment Emergent Surgery) was a 60 year old male with a history of tonsillectomy, seasonal allergies, sleep apnea, hypertension, appendectomy, cholecystectomy, obesity, peripheral edema, adult onset diabetes mellitus, skin rash, proteinuria/gold therapy, excision of eyelid polyps, toe surgery, allergy to penicillin, excoriated insect bites, hyperlipidemia, hypothyroidism, chronic obstructive lung disease, tobacco use and RA. The patient had previously participated in the N49-96-02-023 clinical trial during which he received placebo. After being withdrawn early from this study due to treatment failure, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID on 11 November 1996. Dosage was increased to 300 mg BID 15 days later, on 27 December 1996. Eighty three days later, on , the patient complained of chest pain. The Investigator referred the patient to his primary physician, who started the patient on clarithromycin for possible pneumonia and did a chest x-ray. Twenty six days later, on ,

the patient was hospitalized for a lung mass which was seen on the chest x-ray. Three days following hospital admission, on , 4000 cc of fluid was aspirated from the patient's lungs. Cell differential of this fluid returned cancer cells. The diagnosis of adenocarcinoma of the lung was made and a scan showed metastasis of the liver. Thirteen days following admission, on , a thoracotomy was performed. The patient was mechanically ventilated postoperatively. Seven days later, on , the patient expired due to respiratory failure secondary to carcinoma of the left lung. Concomitant medications included diltiazem, glipizide, gemfibrozil, levothyroxine, docusate, terfenadine, methotrexate, phentermine, fenfluramine, anti-fungal cream and continuous positive airway pressure oxygen. Study drug was discontinued on 15 April 1997. The patient never recovered

15. Patient No. US0073-0060 (Respiratory Insufficiency, Cardiac Failure) was an 85 year old female with a history of removal of benign throat tumor, hypertension, peptic ulcer disease, cholecystectomy, cigarette smoking, post-menopause, osteoporosis, right hip replacement, hypothyroidism, bilateral cataracts, lens implants,and RA. The patient had previously participated in the N49-96-02-023 clinical trial during which she received placebo. After being withdrawn early from this study due to treatment failure, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID on 10 March 1997. Dosage was increased to 300 mg BID four days later, on 14 March 1997 and to 400 mg BID 11 days later, on 25 March 1997. Twohundred and twenty eight days after dose adjustment, on 8 November 1997, the patient was hospitalized for unknown reasons. The patient died 12 days later, on of respiratory secondary to congestive heart failure. Concomitant medications included sulfasalazine, levothyroxine sodium, alendronate sodium, lisinopril, furosemide, and potassium chloride. Study drug was interrupted during hospitalization.

16. Patient No. US0073-0189 (Myocardial Infarction) was a 71 year old female with a history of sleep disturbance, hypertension, irregular heart rate, cholecytecomy, appendectomy, ovarian cyst removed, benign breast cyst removed, cataracts, post-menopausal, anemia, hyperglycemia, hypercholesterolmia, hyperuricemia, and rheumatoid arthritis. The patient had previously participated in celecoxibclinical trial #N49-96-02-022, during which the patient had received either placebo, celecoxib 100 mg BID, 200 mg BID, 400 mg BID or naproxen 500 mg BID. After terminating early due to treatment failure, she was entered into the long-term safety study and began taking celecoxib 200 mg BID on November 21, 1997. Seventeen days later, on December 8, 1997, dosage was adjusted to 400 mg BID. Seventeen days later, on , the patient began experiencing jaw pain that radiated to the chest. The patient was hospitalized with a possible myocardial infarction. Initial cardiac enzymes were elevated. An electrocardiogram revealed septal and lateral wall changes. Treatment included subcutaneous heparin sodium, nitroglycerin, metoprolol tartrate, and warfarin sodium. Three days after admission, , the patient died due to complications from a myocardial infarction. Concomitant medications included methotrexate, folic acid, enalapril, calcium carbonate, vitamin E, lorazepam, multivitamin, digoxin, and prednisolone acetate.

17. Patient No. US0087-0100 (Sepsis, Pneumonitis, Respiratory Insufficiency) was a 66 year old male with a history of hypertension, gastrointestinal upset related to anti-inflammatory medications, reflux esophagitis, gastritis, benign cyst on left hip, osteoporosis, dermatitis, heat rash, diabetes, positive Helicobacter pylori, right medial menisectomy, crush injury to left hand and remote history of peptic ulcer disease, allergy to penicillin, and rheumatoid arthritis. The patient had previously participated in celecoxibclinical trial #N49-97-02-023, during which the patient had received celecoxib 100 mg BID, 200 mg BID, 400 mg BID, naproxen 500 mg BID or placebo BID. After terminating early from this study due to treatment failure, he was entered into the long-term safety study, N49-96-02-024, and began taking celecoxib 200 mg BID on May 6, 1997. Dosage was increased to 300 mg BID, 14 days later, on May 20, 1997 and increased again to 400 mg BID, 4 days after that, on May 24, 1997. One hundred and seventy-four days after dose adjustment , the patient was admitted to the intensive care unit for complaints of shortness-of-breath, dyspnea, left sided weakness and elevated blood pressure. A CAT scan of the lungs showed alveolar edema, chest x-ray revealed peripheral pulmonary fibrosis, presumably secondary to rheumatoid arthritis or long-term methotrexate therapy, and changes consistent with pulmonary edema. And electrocardiogram revealed sinus tachycardia with ST and T sagging in the lateral leads, and a suggestion of left atrial hypertrophy. A CAT scan of the head was negative. Blood cultures revealed enterococcal species. Physical exam was remarkable for crackles in bilateral lung fields almost to the scapular level and slight left arm and leg weakness with slightly diminished reflexes bilaterally. According to the study coordinator, the patient's blood pressure had been elevated to at least 176/86 at his past few

visits and he had been advised to see his primary physician. The patient was started on enalapril maleate, furosemide, and digoxin. Additional treatment for this event included Humulin Insulin, multiple antibiotics, Ventolin, Atrovent, Heparin and famotidine, tracheostomy and mechanical ventilation. The patient died 29 days later, on . The cause of death was determined to be respiratory failure, overwhelming sepsis and the interstitial pneumonitis. Concomitant medications included hydroxychloroquine sulfate, folic acid, glyburide, omeprazole, metformin hydrochloride, calcium and methotrexate. Study medication was interrupted during hospitalization.

18. Patient No. US0110-0006 (Myocardial Infarction) was a 61 year old female with a history of fluid retention, hyperlipidemia, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, tobacco use, triple bypass surgery, arrhythmia, abdominal aortic aneurysm, hysterectomy, thrombocytosis and rheumatoid arthritis. The patient had previously participated in Searle study #N49-96-02-022, during which she received either placebo, celecoxib 100 mg BID, 200 mg BID, 400 mg BID or naproxen 500 mg BID. After successfully completing this study, on December 17, 1996, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID. Dosage was adjusted to 300 mg BID 17 days later, on January 3, 1997, and again to 400 mg BID 35 days after that, on February 7, 1997. Two hundered and twenty days after the last dose adjustment, on , the patient underwent femoral bypass surgery due to a foot ulcer that was caused by poor circulation. The patient was discharged 3 days later, on . Eleven days later, on , the patient was re-hospitalized with complaints of chest pain. The patient underwent cardiac catheterization and angioplasty with stent placement. The patient was discharged 31 days later, on . Seventy-seven days later, on , the patient suffered a myocardial infarction and died. The patient's brother had died earlier in the week. Concomitant medications included prednisone, digoxin, pravastatin sodium, acetylsalicylic acid, furosemide, pentoxifylline, and multivitamins.

19. Patient No. US0116-0042 (Arterial Dissection, Aneurysm) was a 78 year old female with a history of cataracts, lens implants, hypertension, supraventricular tachycardia, angioplasty, appendectomy, hiatal hernia, post-menopause, bilateral metatarsophalangeal repair, allergies to piroxicam and gold, and rheumatoid arthritis. The patient had previously participated in celecoxib clinical trial # N49-96-02- 022, during which the patient had received either placebo, celecoxib200 mg BID on September 25, 1997. After 88 days of treatment, on , the patient was hospitalized with an ascending aortic aneurysm and developed a dissection which was confirmed on repeat CT scanning. Preoperative echocardiogram revealed moderately severe aortic stenosis with a peak gradient of 42. On , the patient underwent an aortic valve replacement with a 21mm St. Jude Mechanical heart valve and ascending aorta and hemi-arch replacement with 24mm Hemashield graft utilizing circulatory arrest and hypothermia. During the procedure, the patient began bleeding from the anterior portion of the proximal anastomosis and developed left ventricular aortic discontinuity from this area. Massive bleeding ensued. Attempts to repair this were unsuccessful and the patient was pronounced dead. The death certificate revealed the cause of death as type I ascending (aortic) arch dissection, artherosclerotic coronary artery disease and critical aortic stenosis. Concomitant medications included sulfasalazine, diltiazem hydrochloride-sustained release, thyroid, Ascriptin, medroxyprogescerone acetate, conjugated estrogens, and digoxin. Study medication was interrupted one day prior to hospitalization.

20. Patient No. US0121-0052 (Sepsis, Pneumonia, Myocardial Infarction) was a 52 year old male with a history of tinnitus, recurring sore throats, decreased hearing, sinus trouble, sores in mouth, glasses, pain behind eyes, depression, headaches, vertigo, fainting spells, occasional chest pain, influenza, cough, chronic obstructive airway disease, pneumonia, obesity, hernia repair, appendectomy, H. pylori, hemorrhoids, gastritis, pedal edema, leg cramps, bursitis, brittle nails, skin rash, hypoglycemia, diabetes mellitus, allergies to penicillamine and cyclosporin, and RA. The patient had previously participated in the N49-96-02-022 clinical trial during which he had received celecoxib 100 mg BID. After successfully completing this study, he was entered into the long-term safety study and began taking celecoxib 200 mg BID on 29 September 1997. Fourteen days later, on 13 October 1997, dosage was increased to 300 mg BID. Four days after that on , the patient presented with shortness of breath which had been present for one month, and had become significantly worse, and was admitted with respiratory distress. Physical examination revealed a blood pressure of 107/50 on dopamine, respiratory rate of 15, which was decreased from 36 previously, and a temperature of 99°F. Lung auscultation revealed crackles in the left base, and a trace of bipedal pitting edema. Pleural fluid and sputum grew Acinetobacter “pneumoniae.” White blood

cell count was 10.5 on admission. Complete blood differential count revealed a left shift with 54 bands. The patient's blood urea nitrogen was 24 and creatinine was 3.3 on admission and rose to 35 and 4.7, respectively, one day after admission. Potassium rose from 4.7 to 6.9 in just a few hours. Aspartate transaminase, which was initially normal, rose to 649. Alanine transaminase rose to 309 and lactate dehydrogenase to 3,272; CK-MB index was 7.9%. Arterial blood gasses were pH 7.06, pC02 of 67, and p02 of 58 on a 7 liter oxygen mask. Pleural fluid showed 14,000 nucleated cells with neutrophilic predominance and glucose of 70 with pH of 7.2. Blood cultures grew a bacillus species. Electrocardiogram revealed sinus tachycardia with an incomplete right bundle branch block and small Q wave in lead III with anterolateral ST changes consistent with possible ischemia. Chest x-ray showed cardiomegaly and a possible pleural effusion on the left. Treatment included intubation and subsequent ventilator support, thoracentesis, insertion of a Swan-Ganz, central venous pressure line, arterial line and Vas-Cath, dopamine in increasing doses, rescue doses of steroids, ceftriaxone, sodium, fluid replacement for dehydration and sepsis, phenylephrine hydrochloride drip, amikacin, and ofloxacin. The patient was found to have gram negative sepsis and pneumonia and subsequently expired one day later on . According to the death certificate, the patient died of an acute myocardial infarction. No autopsy was done. Concomitant medications included methotrexate, prednisone, and folic acid as well as nasal continuous positive airway pressure. Study medication was continued up until the time of death.

21. Patient No. US0139-0009 (Subarachnoid Hemorrhage) was a 57 year old female with a history of dyspepsia, hysterectomy, lumbar spinal fusion, and RA. The patient had previously participated in the N49-96-02-022 clinical trial during which she had received placebo. After successfully completing this study, she was entered into the long-term safety study and began taking celecoxib 200 mg BID on 26 August 1997. Twenty three days later on , the patient was admitted with a grade V subarachnoid hemorrhage. On admission her right pupil was fixed and dilated and she had decerebrate posturing. Apparently, this had occurred at 4:30 in the morning, with onset of emesis and loss of consciousness at that time. She was subsequently intubated and received mannitol and was transferred by ambulance to the hospital. On examination her initial blood pressure was 200/80 and nitroglycerin paste was given to help lower this. Her Glasgow Coma Scale at the time of admission was 4T. A computerized tomography scan revealed diffuse subarachnoid hemorrhage with a large right sided temporal lobe clot; intraventricular hemorrhage; right to left shift; and extensive midbrain compression and swelling. The patient deteriorated and was pronounced brain dead later that same day. Concomitant medications included methotrexate, folic acid, sulfasalazine, and estrogen.