Celecoxib Integrated Efficacy Review:

The efficacy of Cx was addressed in NDA 20-998 by a combination of single-dose and multiple-dose analgesic studies, along with numerous studies in OA and RA. Since 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 efficacy (and its implications for effectiveness) of Cx may, or may not, represent a discussion regarding the theoretical advantages of COX-2 selective or specific agents to function as an analgesic and anti-inflammatory compound. Only time, and more compounds of similar characteristics, will answer these questions.

Nevertheless, the efficacy of Cx is a very important issue since it will ultimately dictate where this compound fits in the clinician's armamentarium to treat pain and diseases such as OA and RA. According to the currently understood theory of the role of COX-2 in health and disease, the efficacy of Cx must, at least, equal that of available comparator therapies (i.e. commonly called NSAIDs).

Pain

For the "general purpose" management of acute pain the usual requirement is (replicated) evidence of efficacy in at least two different type of pain models. Replicated evidence of efficacy in single-dose studies when patients will not need more than one or few doses (e.g., dental pain) and replicated evidence of efficacy in multiple doses over several days studies in patients requiring short-term therapy (e.g., post surgery).

During the development program of Cx, six studies were conducted to support the management of pain indication in accordance with the above requirements. Four single dose studies in the dental pain model (025, 027, 070, 005) and two multiple dose studies in the post orthopedic/general surgery model (028, 029,).

Of the four dental pain studies, three are considered to be pivotal (study 005 had a single blind design). In these studies, Cx at doses of 100 mg SD (Studies 027 and 070), 200 mg SD (Studies 025, 027 and 070), and 400 mg SD (Study 070) showed statistically significantly greater improvement in pain compared to placebo beginning at 45 minutes to 1 hour postdose and continuing through 7 to 8 hours postdose for the time specific efficacy measures. Time to Rescue Medication was statistically significant longer compared to placebo with Cx doses of 50 mg, 100 mg, 200 mg and 400 mg. Shorter Time to Perceptible Pain Relief compared to placebo was statistically significant for only the 200 mg dose (Studies 025 and 027). It is important to note that the NSAID comparators (ibuprofen 400mg and naproxen sodium 550mg) demonstrated a more rapid onset of analgesia and a statistically significantly greater peak response than Cx at all doses studied (25 mg, 50 mg , 100 mg, 200 mg, and 400 mg) beginning

at 30 to 45 minutes postdose and continuing trough 3 to 5 hours postdose for the time specific efficacy measures.

In the two multiple dose post general/orthopedic surgical pain studies interim analyses (not included in the protocol) were conducted. The reason given was that: "the enrollment had been slower than expected and the dropout rate had been higher than expected, raising concerns that the model was not behaving as anticipated". Study 029 (post general surgery) was terminated following the interim analysis because neither Cx nor the comparator (Darvocet-N) separated statistically from placebo. In the multiple dose post-orthopedic surgery trial (028) the only statistically significant differences favoring Cx over the placebo were at a dose of 200 mg for the pain relief plus pain intensity difference (PRID) measurement, at 6, 7, and 9 hours when using BOCF technique and some scattered and inconsistent finding of a significant efficacy for the other time specific efficacy measures. Therefore, no substantial evidence has been demonstrated in the multiple dose post general/orthopedic surgical pain studies to support the management of pain indication.

Other acute pain assessments have been attempted in three OA studies which pain was first measured at bedtime beginning on the first study day and continuing for 7 days. Pain was measured at bedtime and we actually have no information available in regard to the time elapsed between ingesting the drug and the pain measuring. These three OA studies demonstrate some positive efficacy results of a multiple-dose administration of Cx over a week period. These results can be regarded as supportive but still inconclusive evidence of efficacy.

A key issue here is whether a new molecular entity can gain a management of acute pain indication based only on evidence from single dose studies in one type of a pain model. Although the results of the OA studies lend some general support to idea that Cx can have an analgesic effect, the evidence of its utility for acute analgesia is weak. Celecoxib "won" in three pivotal, single-dose dental pain studies, but it appeared to be less effective than ibuprofen or naproxen sodium, and it failed in showing statistically significant efficacy in the treatment of pain in two multiple dose, 3-5 day post operative trials.

However, it must be noted that the post major orthopedic surgery model may not be an appropriate model for the study of drugs such as Cx. Of the 246 patients on Day 1, only 48 patients entered the Day 2 and this number was further reduced by day 5 of the study. Therefore, the planned statistical tests for variables obtained on Day 2 through Day 5 were not carried out due to the small number of patients remaining in the study. Moreover, this pain model was not validated by the active control Darvocet-N® 50 (2 tablets) QID PRN beyond the first 24 hours for the same reason, thus implying that the severity of pain involved in this model beyond 24 hours post surgery is too high for the medications tested. However, the withdrawal rate occurred equally in all treatment groups but this observation may relate more to the limited length of hospital stay mandated by managed care practices.

OA

Efficacy in the treatment of the signs and symptoms of OA has been demonstrated in NDA 20-998 by adequate and well-controlled trials. Endpoints in these trials that helped to establish (but not limited to these) efficacy include the patient and physician's globals (Appendix Table A.7-A.8), assessment of pain-categorical/VAS (Appendix Table A.9-A.10), WOMAC scores-subscales and composite (Appendix Table A.11-A.18) along with the OSI Index (Appendix Table A.19) and time to withdrawal due to lack of arthritis effect (Appendix Table A.20-A.21).

There was generally a dose-response between Cx 50 mg BID and higher doses, but not between Cx 200 mg BID and lower doses. Patients were generally still symptomatic. Treatment responses generally appeared durable for 12 weeks but some endpoints in certain trials (i.e. primary endpoints-Patient Assessment of Arthritis Pain) suggest a waning of this response over time. Celecoxib, given as a single evening dose of 200 mg is equally as efficacious as 100 mg BID by the same endpoints noted above. It is difficult to draw any conclusions from the non-flare trials. Celecoxib, especially at the higher doses, is comparable in efficacy to naproxen.

Therefore, the following conclusions regarding Cx and treatment of the signs and symptoms of OA are drawn from the information (ITT/LOCF) presented in the randomized clinical trials:

- Cx from 100 mg BID to 200 mg BID is consistently efficacious vs. placebo
- Cx 50 mg BID is not consistently efficacious vs. placebo
- Cx (200 mg BID) is not consistently more efficacious vs. Cx (100 mg BID)
- Cx (100-200 mg BID) has efficacy comparable to Naproxen 500 mg BID
- Cx (100 mg BID) is as efficacious as Cx (200 mg QD)

RA

Efficacy in the treatment of the signs and symptoms of RA has been demonstrated in NDA 20-998 by adequate and well-controlled trials. Endpoints in these trials that have helped to establish (but not limited to these) efficacy include the patient and physician's globals (Appendix Table A.34-A.35), assessment of pain-categorical/VAS (Appendix Table A.40), Tender and Painful Joint Counts (Appendix Table A.36), Swollen Joint Counts (Appendix Table A.37), ACR 20 Responder Index (Appendix Table A.38) ACR 50 Responder Index (Appendix Table A.39) and HAQ Functional Index Disability Index (Appendix Table A.42). Of note, Cx (and naproxen), did not seem to effect the acute phase responses as witnessed by a lack of effect on C-reactive protein levels (Appendix

Table A.41). Celecoxib, in study 012, also did not seem to effect ESR or Serum Amyloid A levels.

There was a general (though not universal) dose-response between Cx 100 mg BID and higher doses, but not between Cx 400 mg BID and lower doses. Treatment responses generally appeared durable for 12 weeks but some endpoints in certain trials (i.e. primary endpoints-Physician and Patient's Globals) suggest a waning of this response over time. Generally speaking, fewer patients withdrew for lack of treatment effect at the higher doses of Cx (Appendix Table A.43); all doses were superior to placebo in this regard. Placebo patients also tended to withdraw earlier from studies than Cx-treated patients (Appendix Table A.44).

Neither the "evaluable" nor the "observed" cohort analyses for Cx generally demonstrated a consistent statistically significant difference from placebo at weeks 6 and 12. This was also the overall pattern seen with naproxen, but results were inconsistent between trials. Celecoxib, especially at the higher doses, is comparable in efficacy to naproxen.

Therefore, the following conclusions regarding Cx and treatment of the signs and symptoms of RA are drawn from the information (ITT/LOCF) presented in the randomized clinical trials:

- Cx from 100 mg BID to 400 mg BID is consistently efficacious vs. placebo
- Cx 200 and 400 mg BID is frequently more efficacious vs. Cx 100 mg BID
- Cx 200 mg BID and 400 mg BID generally have comparable efficacy
- Cx (100 mg-400 mg BID) has efficacy comparable to Naproxen 500 mg BID

In summary, Cx has demonstrated in adequate and well-controlled trials that it is effective in the treatment of the signs and symptoms of RA and OA. However, Cx has not yet demonstrated that it is effective in the management of pain. The failure in the analgesia trials results from the multiple-dose trials. It is anticipated that future clinical trials of this nature will clarify these analgesia issues adequately enough to support a claim for the management of pain.

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 Safety Review

This ISS will also strive to incorporate much of the **Cx 120-Day Safety Update** which summarizes the safety information obtained after **the data cutoff date** for the Integrated Summary of Safety Information submitted in the original NDA (November 21, 1997) through **July 24, 1998** on a total of 6323 patients/subjects. As discussed later, of the 6323 patients/subjects, 5629 received Cx and 1130 were new patients.

The intent of the following sections is to look for trends suggesting an increased incidence of a given adverse event, based on multiple line of (indirect) evidence. This is, of course, the nature of a safety review.

Duration/Degree of Exposure to celecoxib in original NDA:

A total of 51 trials were submitted to support NDA 20-998. There were 29 clinical pharmacology and 22 phase 2/3 clinical efficacy trials. Of these, 13 clinical trials were performed to compare Cx with other NSAIDs. These 51 trials have been divided into 3 basic types of studies (see Table 1).

Considering all the Cx trials in **Phase 1** (**includes trials 001, 006, 009, 018, 019, 037, 044, 084, 088, 003, 004, 010, 014, 015, 026, 032, 033, 043, 065, 069, 017, 038, 039, 040, 050, 051, 072, 016, 036**) the following

numbers of patients (unique individuals) received at least one dose of study medication as indicated in Table 11 below:

Table 11. Number of Subjects in NDA 20-998: Phase 1 Trials

Dose (total daily)	No. patients	% Total Cx
<50 mg	12	1.5
100 mg	67	8.6
200	381	49.0
300	10	1.3
400	253	32.5
600-1200	55	7.1
TOTAL	778	100.0

Considering all the Cx trials in **OA** (includes trials 013, 047, 020, 054, 021, 060, 087, 062, 071, 042), the following numbers of patients (unique individuals) received at least one dose of study medication; the proposed length of exposure is indicated in table 12 below:

Table 12. Number of Patients in NDA 20-998: Osteoarthritis Trials

Dose	No. patients[1]	Trial length (weeks)	% Total Cx
25 mg BID	101	4	2.3
40 mg BID	73	2	1.7
50 mg BID	671	12	15.3
100 mg BID	76	2	1.7
	101	4	2.3
	821	6	18.6
	644	12	14.7
200 mg QD	454	6	10.3
200 mg BID	73	2	1.7
	1114	12	29.2
400 MG BID	99	4	2.3
TOTAL	4227	-	100.0

1. Studies 062 and 071 had patients with both OA and RA, only OA patients included here.

Considering all the Cx trials in **RA** (includes trials 022, 023, 041, 012, 062, 071), the following numbers of patients (unique individuals) received at least one dose of study medication; the proposed length of exposure is indicated in table 13:

Table 13. Number of Patients in NDA 20-998: Rheumatoid Arthritis Trials

Dose	No. patients[1]	Trial length (weeks)	% Total Cx
40 mg BID	81	4	3.9
100 mg BID	468	12	22.3
200 mg BID	82	4	3.9
	326	24	15.5
	624	12	29.7
400 MG BID	82	2	3.9
	435	12	20.7
TOTAL	2098	-	100.0

1. Studies 062 and 071 had patients with both OA and RA, only RA patients included here.

Table 14 breaks the distribution of patients who received various doses of Cx in the North American (NA) and International Arthritis Trials into males and females. Again, it is clear that the majority of patients studied were females.

Table 14. Number of Male/Female Patients in NDA 20-998: North American Trials

	Males			Females		
Disease	N. American	International	Combined	N. American	International	Combined
RA	473	79	552	1297	247	1544
OA	1245	100	1345	2689	246	2935
Total	1718	179	1897	3986	493	4479

Considering all the Cx trials in **Pain** (includes trials 005, 025, 027, 070, 028, 029), Table 15 shows the numbers of patients (unique individuals) who received at least one dose of study medication:

Table 15: Number of Patients in NDA 20-998: Pain Trials

Dose	No. patients	% Total Cx
≤ 50 mg SD	135	18.0
100 mg SD	155	20.7
200 mg SD	156	20.9
400 mg SD	85	11.4
100 mg BID, prn	113	15.1
200 mg BID, prn	104	13.9
TOTAL	748	100.0

Tables 11, 12, 12 and 15 above do not include the long-term extension trial (024) which was discussed earlier. As noted in Table 16 below, there are some differences between the number of individuals treated with Cx according to the NDA Tables 2.9 and 2.10 (see *Appendix Table A.46)* and the tables 11-15 noted above:

Table 16. Overall Number of Subjects/Patients in NDA 20-998

Trials in:	No. patients		
	NDA Review	Cx Table 2.9	Cx Table 2.10
Phase 1	778	1023	723
OA	4227	4280	4151
RA	2098	2096	2086
Pain	748	748	746
TOTAL	7851	8147	7706

The number of patients listed under the category "NDA Review" in table 16 above, represents the number of "unique" patients presumably randomized, whereas the number of patients in Cx Table 2.10 (see Appendix Table A.46) presumably represents the number of unique individuals who actually received Cx (i.e. the denominator). The number of patients in Cx Table 2.9 (see Appendix Table A.46) represents "treated" patients but patients may be represented more than once here. For example, the largest discrepancy is in the Phase 1 data and those patients studied who had OA. The Phase 1 data difference largely reflects the fact that many of these trials were of a cross-over nature. Of note, there were 127 patients that enrolled in one arthritis efficacy study and subsequently enrolled in a later arthritis efficacy study.

> ***Reviewer's comment: It is not unusual that numbers of patients do not match on all the various tables throughout the NDA. It is not possible, in this review, to completely identify the cause of these differences (i.e. whether some tables include only randomized vs. dosed patients, or both). However, most of the time these differences are small; significant differences are noted in the review.***

Regarding the **duration of exposure to Cx** at various doses, it is clear that the bulk of the exposure, both in terms of number of patients and the duration of treatment resulted from patients with either OA or RA (***Appendix Table A.47.1-.2***) in the long-term, open label study (024) previously discussed. The Phase 1 and Pain studies were mostly single-dose experiences or exposures for around 2 weeks (maximum). It should be noted that some patients transferred into the open label study well over one year before the cutoff date (November 21, 1997) while other patients were transferring at the time of the cutoff date. It is necessary to understand that evaluating the extent of exposure in this ongoing study is complicated by short durations of exposure due to dropouts and patients who are still active at the cutoff date.

The duration of exposure to **the highest (currently) proposed dose of Cx (200 mg BID)** shows (Appendix Table A.47.2, subtable 3.4) the following:

- 1074 patients received Cx for 92-180 days
- 430 patients received Cx for 181-270 days
- 316 patients received Cx for 271-360 days
- 172 patients received Cx for 361-450 days

There are patients who have received Cx for longer periods of time, and as noted elsewhere in this review, there is an ongoing, large open-label safety/efficacy trial (024) in progress. Furthermore, as can be seen in the tables, there are substantially more patients who have been exposed to higher or lower doses of Cx than 200 mg BID. Of particular note are the 156 patients who have received Cx at 400 mg BID for 271-360 days. These exposures to Cx **clearly exceed ICH recommendations.**

Reviewer's comment: Since the bulk of the exposure to Cx is in patients with OA and RA, this safety review will mostly focus on these populations. However, safety issues in the Phase 1 and Pain experiences will be addressed where appropriate.

Although the **inclusion and exclusion criteria** varied among these arthritis studies, it is important to remember that patients were generally excluded from participation if they had active GI disease, a chronic or acute renal or hepatic disorder, or a significant coagulation defect. In addition, patients were excluded if they had any laboratory abnormalities at screening considered by the Investigator to be clinically significant or they had known hypersensitivity to COX-2 inhibitors, sulfonamides, or NSAIDs.

Three studies performed in the United States and Canada included patients with either OA or RA. Two of these (Studies 062 and 071) were primarily designed to compare the incidences of UGI ulceration between celecoxib and a total of three NSAID comparators (diclofenac, ibuprofen, and naproxen). In these studies, UGI endoscopy was performed prior to dosing and after 4, 8, and 12 weeks of study drug administration (see UGI Safety Review). The third study (Study 024), as noted elsewhere in this review, was a long-term open-label study that is continuing at the time of this submission. Patients who participated in an earlier arthritis study were eligible to enroll into study 024 for up to two years.

Duration/Degree of Exposure to celecoxib in 120- Day Safety Update:

The 120-Day Safety Update includes data from the ongoing long-term, open label study (024) reported in the ISS along with data not included in the original NDA from six controlled clinical studies (Table 17, below). Demographic and adverse event information derived from clinical databases are provided for these studies, as well as information on serious adverse events and deaths. Ten additional studies are that are also currently ongoing and also not included in the original NDA are added this update. Only information on serious adverse events and deaths in these studies (Table 17, below) is summarized in the Update.

Table 17. Studies Included in 120-Day Safety Update

Type of Study	No. of Studies	Study Numbers
Demographics, adverse events, SAEs and deaths		
Phase 1		
Single dose	**1**	**007**
Multiple dose	**1**	**079**
Long-term open label	**1**	**024***
Surgical Pain		
Single dose	**2**	**082, 083**
Multiple dose	**2**	**085, 086**
SAEs and deaths		
Ex-U.S. long-term safety	**1**	**I49-97-02-058**
Ongoing analgesia	**3**	**E49097-02-074** **E49-97-02-075** **I49-97-02-078**
Alzheimer's disease	**2**	**IQ5-97-02-001** **Iq5-98-02-004**
Cancer chemoprevention	**2**	**IQ4-96-02-001** **NQ4-97-02-003**
Japanese studies	**2**	**41771/Rpil** **41771/Opil**
Total	**17**	

*** The NDA ISS contained data for 4499 patients, the 120 Update contains data for 5155 patients.**

The total enrollment of patients and subjects receiving celecoxib in all studies for which data from clinical databases are reported in this Safety Update is 5629 (see **Figure 1**, below). This total contains 120 subjects receiving celecoxib in the Phase I single dose trial (study 007); 24 subjects receiving celecoxib in the Phase I multiple dose trial (study 079); 5155 patients receiving celecoxib in the long-term, open-label study (which represents 656 new patients since the ISS report); and 330 patients receiving celecoxib in previously unreported surgical pain studies (studies 082, 083, 085, 086). Therefore, of the 5629 patients/subjects who received Cx, 1130 (656+330+144) represent new individuals not previously noted in the ISS of the NDA.

Figure 1. Exposure to Cx in Clinical Studies Reported in this Safety Update

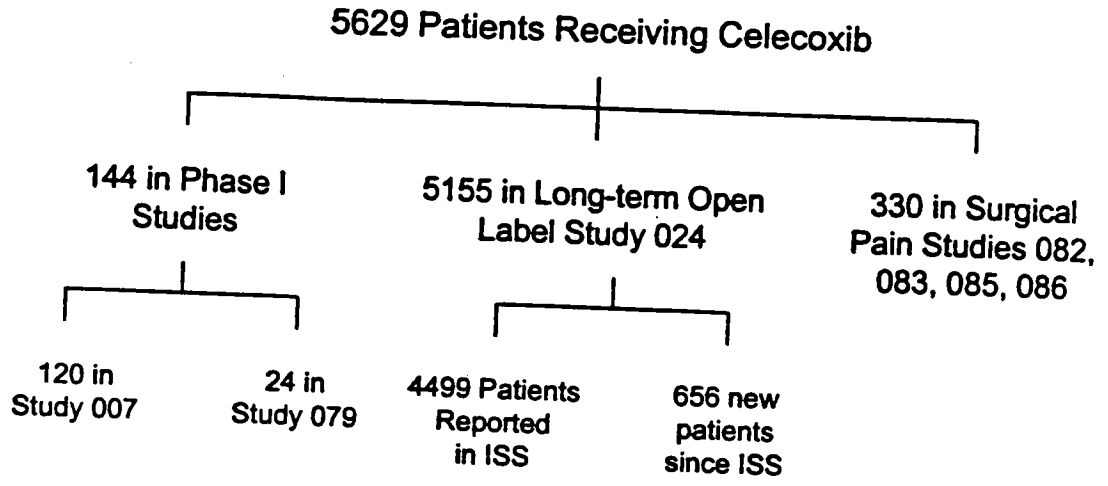

Table 18 further summarizes the overall duration of exposure to Cx with this safety update.

Table 18. Duration of Exposure in Safety Update, Open-Label Study (024)

Days of Exposure (Long-term Open Label Trial)	No. of Patients Receiving Celecoxib at Any Dose and Regimen (ISS)	No. of Patients Receiving Celecoxib at Any Dose and Regimen (Safety Update)
≥ 1	4499	5155
≥ 15	4369	5071
≥ 43	4054	4848
≥ 78	3684	4609
≥ 92	3517	4497
≥181	2363	3971
≥271	1573	3282
≥361	965	2443
≥451	293	1676
≥541	0	1165
≥631	0	615
≥721	0	124
Total	4499	5155

Expressed in terms of patient years, table 19summarizes the exposure in study 024.

Table 19. Patient-Years of Exposure in Safety Update, Open-Label Study

	50 mg BID	100 mg BID	200 mg BID	300 mg BID	400 mg BID	Other*	Any Dose
ISS	74.8	518.8	1271.0	340.1	465.2	2.5	2672.4
Safety Update	74.8	844.1	2520.1	599.5	960.0	3.4	5001.9

*These patients have celecoxib doses of 300 mg AM/200 mg PM; 200 mg AM/100 mg PM; 200 mg AM/300 mg PM; 400 mg AM/300 mg PM; 100 mg QD; 100 mg OD; 100 mg TID; or 200 mg OD.

As can be seen, the majority of exposure to Cx occurred in this long-term, open-label study (5155 patients with 5002 patient-years of exposure, representing 2329.5 additional patient-years since the sponsor ISS was written); the remaining new exposure represents one single dose Phase I study, one multiple dose Phase I study, and four surgical pain studies (two single dose and two multiple dose).

> ***Reviewer's comment:*** ***It should be noted that of the 5155 patients currently represented in the long-term, open-label safety update, 1966 have withdrawn while 3189 are still active. 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 I 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.***

Demographics:

The basic demographic characteristics for all the arthritis studies (i.e. North American and International) is presented in ***Appendix A.51***. Once again, as noted in the efficacy descriptions for OA and RA, there did not appear to be any significant differences between the Cx groups nor between Cx and placebo or active control groups. Patients studied were mostly all older than 40 years (mean-median; range 58-63 years); the RA patients tend to be younger than the OA population by about 8 years (see OA/RA efficacy sections). The overall **mean age** in patients receiving Cx was 59.5 years, compared with 60.0 years in placebo patients and 58.8 years in patients receiving active control (naproxen, diclofenac, or ibuprofen). In all treatment groups, **female** patients predominated, with the proportion ranging from 66.2% to 72.7%. The patients in these studies were predominantly **Caucasian** (>82% in all treatment groups), followed by Black and then Hispanic patients. For female patients, **mean weights** across treatment groups ranged from 76.7 to 88.6 kg. Mean weights of male patients ranged from 88.0 to 97.0 kg.

On the other hand, the phase 1 and analgesic populations were more of a mixture in terms of age, ethnicity and gender (data not shown here). For example, the dental pain patient was approximately 23 years old, the surgical patient approximately 48 years old, while the phase 1 single and multiple-dose and drug interaction subject tended to be male. Similarly, due to the small number of subjects in the hepatic and renal trials, there were imbalances in demographics across treatment groups mostly with respect to ethnicity and gender.

The demographic characteristics of patients who received study medication in the long-term study in the 120 Day-Safety Update were similar to those for the long-term, open-label patients at the time of the ISS. For example, the mean age for OA patients was 61.6 years and for RA patients was 54.8 years (overall 58.6 years). The percent of females was 67.7% for OA patients and 72.9% for RA patients (overall 69.9%). The percent of Caucasians was 88.3% for OA patients and 86.1% for RA patients (overall 87.4%). Mean weights for OA patients were greater than for RA patients among both females (84.0 kg vs. 74.6 kg) and males (95.8 kg vs. 87.9 kg).

Platelet Safety:

Reviewer's comment: For a more in-depth review on this subject, the interested reader should see the Gastrointestinal and Coagulation Drug Products consult.

A major physiologic effect of nonspecific COX inhibition with important clinical consequences is the inhibition of platelet function. Thrombogenic stimuli such as collagen initiate aggregation of platelets and their production of thromboxane A_2 (TxA_2), which in turn promotes further aggregation. The production of TxA_2 during platelet activation is mediated by COX and thromboxane A_2 synthase. In the case of platelets, which are anucleate cells that cannot produce COX-2, TxA_2 production is exclusively a function of the activity of COX-1. Nonspecific COX inhibitors such as aspirin and NSAIDs inhibit the production of TxA_2 via their effect on COX-1 and thereby impair the ability of blood to clot in response to mucosal injury (such as ulceration) or insults to vascular endothelial integrity

The clinical effects of NSAID-induced platelet dysfunction consist of increased mucosal bleeding, such as from GI tract lesions, prolonged surgical bleeding, and additive risk of significant or life-threatening bleeding in patients taking anticoagulants. Other clinical problems associated with platelet dysfunction include increased bruising and unexplained anemia. This anemia may, in many cases, be a dual effect of NSAIDs; first, NSAIDs can produce GI mucosal injury which does not manifest as an overt bleeding ulcer. Second, these lesions may then lead to chronic, low grade blood loss exacerbated by NSAID-induced platelet dysfunction, resulting in anemia. In addition to anemia, characteristic

clinical laboratory measures of NSAID-induced platelet dysfunction include reduced platelet aggregation and prolongation of bleeding time. . Therefore, studies were conducted to evaluate the hypothesis that since Cx inhibits COX-2 and has no apparent COX-1 inhibitory activity at therapeutic (and supratherapeutic) concentrations, it would not be expected to affect platelet function.

Four clinical studies were specifically designed to compare the effects of Cx with those of NSAIDs on platelet aggregation, thromboxane production, and bleeding times, and to correlate these effects with plasma levels of Cx. These prospective studies were supplemented by retrospective analysis of the overall clinical database to determine (1) the incidence and characteristics of adverse events related to bleeding-related adverse events; (2) general effects on hematologic and coagulation clinical laboratory parameters; and (3) a potential dose-response effect of Cx on these measures.

The following table (from Text Table 106, ISS) describes the main features of the four studies undertaken to assess the effects of Cx on platelet function, and a fifth study that included platelet measures.

Table 20. Studies to Assess Platelet Function in NDA 20-998

Study Number	Population	Treatment Groups and Regimens	Treatment Period	Outcome Measures
009 (n=37)	Healthy Subjects	Plc Cx 100 mg BID Cx 400 mg BID Cx 800 mg BID Ibuprofen 800 mg TID	24 hours following single dose	Platelet aggregation, bleeding time, serum TxB_2 and plasma PGE_2 levels
026 (n=6)	Healthy Males	Cx 40 mg BID Aspirin 650 mg SD	Cx for 6 days, followed by single dose of aspirin	Platelet aggregation and whole blood TxB
032 (n=24)	Healthy Subjects	Plc Cx 60 mg BID Naproxen 500 mg BID	Single dose followed by 7.5 days of multiple dosing	Platelet aggregation, bleeding time and serum TxB_2
065 (n=51)	Healthy Subjects	Plc Cx 600 mg BID Diclofenac 75 mg BID Ibuprofen 800 mg TID	7.5 days	Platelet aggregation, bleeding time and serum TxB_2
015 (n=48)	Healthy elderly and young subjects	Plc Cx 200 mg BID	10 days	Platelet aggregation, platelet count

As can be seen in table 20, a principal feature of these studies is that Cx was evaluated at doses exceeding the "recommended" clinical dose range for anti-inflammatory and analgesic efficacy. Celecoxib at doses as high as 800 mg single dose and 600 mg BID were evaluated, compared to the recommended clinical dose of 100 mg BID to 200 mg BID noted in the OA and RA efficacy sections of this review.

To determine the effect of treatments on platelet function, aggregation to collagen and arachidonate were measured as primary variables. Arachidonate aggregation is considered a more sensitive measure of COX-1 effect since it entirely depends on the ability of the platelet to convert the arachidonate to TxA_2, while collagen aggregation is not entirely mediated through this pathway. In these studies thromboxane B_2 (TxB_2) is measured as a surrogate marker of platelet TxA_2 because it is a stable, easily measured metabolite of TxA_2. Other aggregating agents were also used, such as U46619, a TxA_2 mimetic, and adenosine diphosphate (ADP), as secondary agents to validate the aggregation assays. The PGE_2 assay, based on the methodology of Patrignani et al, measured PGE_2 levels following *ex vivo* addition of lipopolysaccharide, as an index of the COX-2 activity of the blood.All studies with placebo groups were designed and powered to show differences between active treatments and placebo responses.

Of note, in Study 009, there was no apparent correlation between Cx plasma AUC_{0-24} or C_{max} and platelet aggregation to collagen or arachidonate. In Study 032, linear regression analysis showed no significant correlation between plasma concentration and platelet aggregation or bleeding time ($p>0.129$). A weak correlation was seen ($r=0.3676$, $p=0.0385$) between plasma concentration and TxB_2 levels on Day 10.

In Study 065, there were two individuals who had markedly high plasma concentrations of Cx. The Day 8 trough level of one subject (065-US001-0040) was 4070 ng/mL vs. a group mean of 2922 ng/mL. One subject (0065-US001-0012) had Day 8 plasma concentrations that were approximately 5 times higher that those observed for the rest of the subjects. His Cx plasma concentration peaked at 16,300 ng/mL, compared to a group mean C_{max} of 4550 ng/mL. The reasons for the high plasma concentrations in these two subjects are not known. Despite the high Cx levels, both subjects were asymptomatic and had normal platelet function.

Preclinical pharmacology studies characterized the enzyme specificity of celecoxib. The half-maximal inhibitory concentration (IC_{50}) for COX-2 is 0.04 μM, and for COX-1 is 15 μM (5720 ng/mL). None of the metabolites of Cx are active against either COX-1 or COX-2. Although this *in vitro* level only represents half-maximal inhibitory concentrations and not full inhibitory activity (IC_{80}) and therefore can only roughly be extrapolated to full inhibitory activity *in vivo*, it is a helpful figure, since **it suggests that clinically some degree of COX-1 inhibition may be possible but is highly unlikely.** Results from the platelet studies indicate that plasma levels of Cx (high enough to inhibit COX-1 activity) are only rarely achievable even with supratherapeutic doses (i.e. 600 mg BID or three-times the maximal therapeutic dose). Moreover, even in the unusual event where extremely high plasma concentrations of Cx were achieved, there was no consistent effect on platelet aggregation or bleeding time.

In summary, the results of these studies demonstrate that, 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. In contrast,

therapeutic doses of NSAIDs (ibuprofen, diclofenac, naproxen and aspirin), all significantly reduced platelet function compared to placebo. Individual variability of inhibition of platelet aggregation was observed. The data are consistent with the conclusion that Cx is a specific COX-2 inhibitor without evidence of COX-1 inhibition at higher than therapeutic doses.

Bleeding time, as evaluated in three of these studies (009, 032, 065), also revealed that Cx did not significantly increase bleeding time whereas the active controls did when compared to placebo. However, the technical variability of the test, limits the overall interpretation of these results.

Serum TxB_2 levels were reduced by the active controls but not consistently by Cx; then only to levels not sufficient to 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 were reported, including (as have been noted elsewhere in this review) MIs which occurred at a slightly higher rate in Cx treated elderly females. Again, the requirement that patients that require thromboprophylaxis may still require low dose aspirin or other antiplatelet effects.

Upper Gastrointestinal Safety Review:

Reviewer's comment: The following in intended only as a summary of this portion on the question of the upper GI safety of Cx. The interested reader is referred to the more detailed GI consultant review.

Central to the hypothesis of the Cx clinical program (and to the theory of COX-2), is that Cx will have anti-inflammatory and analgesic effects (through COX-2 inhibition) but without the deleterious GI effects of NSAIDs (through COX-1 inhibition). To "prove" this hypothesis, studies with Cx focused on two primary outcomes in assessing GI mucosal toxicity: development of gastroduodenal ulcers and erosions (endoscopy) and the occurrence of clinically significant UGI events

Endoscopy:

To address the first question, there were six clinical studies in which UGI endoscopy was performed over 10,500 times in over 4,500 patients to characterize directly the ulceration rate associated with Cx at differing doses in comparison with NSAIDs and placebo. These studies are briefly summarized in the following table:

Table 21. Upper GI endoscopy Studies in NDA 20-998

Study Number	*Population*	*Treatment Groups (number treated)*	*Endoscopy Schedule*	*Outcome Measures*
014 (pilot study) (n=128)	Healthy subjects/ North America	- Placebo (32) - Cx 100 mg BID (32) - Cx 200 mg BID (32) - Naproxen 500 mg BID (32)	- Baseline - 7 days	Gastroduodenal ulceration incidence at 7 days
021 (n=1215)	Patients with OA/ North America	- Placebo (247) - Celecoxib 50 mg BID (258) - Celecoxib 100 mg BID (240) - Celecoxib 200 mg BID (237) - Naproxen 500 mg BID (233)	- Baseline - 12 weeks	Gastroduodenal ulceration incidence over 12 weeks
022 (n=1149)	Patients with RA/ North America	- Placebo (231) - Celecoxib 100 mg BID (240) - Celecoxib 200 mg BID (235) - Celecoxib 400 mg BID (218) - Naproxen 500 mg BID (225)	- Baseline - 12 weeks	Gastroduodenal ulceration incidence over 12 weeks
041 (n=655)	Patients with RA/ International	- Celecoxib 200 mg BID (326) - Diclofenac 75 mg BID (329)	- 24 weeks	Gastroduodenal ulceration incidence over 24 weeks
062 (n=537)	Patients with OA or RA/ North America	- Celecoxib 200 mg BID (270) - Naproxen 500 mg BID (267)	- Baseline - 4 weeks - 8 weeks - 12 weeks	Gastroduodenal ulceration incidences over 4, 8, and 12 weeks
071 (n=1099)	Patients with OA or RA/ North America	- Celecoxib 200 mg BID (366) - Diclofenac 75 mg BID (387) - Ibuprofen 800 mg TID (346)	- Baseline - 4 weeks - 8 weeks - 12 weeks	Gastroduodenal ulceration incidences over 4, 8, and 12 weeks

As can be seen in the table above, not all the studies included a baseline endoscopy. Study 041 was designed to mimic "clinical practice" in this regard since most of the time clinicians are unaware of any endoscopic findings when they initiate therapy with NSAIDs.

In all endoscopy procedures, the gastric and duodenal mucosae were examined and graded separately, using the scale shown below. In the ulcer analyses, a patient was counted as having a gastroduodenal ulcer if either a gastric or duodenal ulcer (or both) was present.

Endoscopy scoring for stomach and duodenum

Score	Description
0	No visible lesions
1	1-10 petechiae
2	>10 petechiae
3	1-5 erosions*
4	6-10 erosions*
5	11-25 erosions*
6	>25 erosions*
7	Ulcer**

* An erosion was defined as any break in the mucosa without depth.
** An ulcer was defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth.

The results of these endoscopic studies are summarized in table 22 below.

Table 22. UGI Endoscopic Ulcers in NDA 20-998

Treatment[1]	Cumulative Ulcer Incidence at Study Endpoint Only: % (no. with ulcer/total known)					
	014 *(7 days)*	*021* *(12 weeks)*	*022* *(12 weeks)*	*041* *(24 weeks)*	*062* *(12 weeks)*	*071* *(12 weeks)*
Placebo GD G D	0 (0/32) - -	4 (4/106) 4 (4/106) -	4 (4/99) 3 (3/99) 1 (1/97)	NA	NA	NA
Cx 50 mg BID GD G D	NA	5 (8/164)[3] 5(8/164) -	NA	NA	NA	NA
Cx 100 mg BID GD G D	0 (0/32)[3] - -	5 (7/155)[3] 5 (7/155) -	6 (9/148)[3] 4 (6/147) 2 (3/147)	NA	NA	NA
Cx 200 mg BID GD G D	0 (0/32)[3] - -	9 (13/150)[3] 7 (10/148) 2 (3/148)	4 (6/145)[3] 3 (4/144) 1 (2/144)	4 (8/212)[2] 2 (5/212) 2 (4/212)	9 (18/211)[3] 6 (12/205) 4 (8/203)	9 (25/294)[4] 8 (23/293) 1 (3/275)
Cx 400 mg BID GD G D	NA	NA	6 (8/130)[3] 5 (7/130) 1 (1/129)	NA	NA	NA
Nap500 mg BID GD G D	19 (6/32) 19 (6/32) 0 (0/32)	23 (34/146) 18 (25/141) 8 (11/40)	26 (36/137) 22 (29/134) 6 (8/128)	NA	41 (87/214) 37 (74/202) 12 (19/158)	NA
Diclo 75 mg BID GD G D	NA	NA	NA	15 (33/218) 11 (24/218) 7 (15/217)	NA	12 (36/106) 9 (27/301) 5 (14/287)
Ibupro 800 TID GD G D	NA	NA	NA	NA	NA	28 (78/276) 23 (60/259) 9 (22/238)

1. GD=gastroduodenal; G=gastric; D=duodenal: NA=not applicable.
2. $p < 0.05$ vs. diclofenac
3. $p < 0.05$ vs. naproxen
4. $p < 0.05$ vs. ibuprofen

In reviewing the table above, it should be kept in mind that studies 062 and 071 had scheduled endoscopies at weeks 4, 8 and 12 whereas the other studies only had endoscopies at study endpoint; all studies included patients endoscoped "for cause" or those evaluated at "early termination". One of the reasons these two studies had more frequent scheduled endoscopies was to address concerns that less frequent monitoring would miss lesions; the data above would suggest this is only the case for naproxen.

> ***Reviewer's comment: Regarding endoscopic ulcers, Cx at the wide range of doses studied is generally significantly different than comparator NSAIDs (the exception being diclofenac in study 071) and similar to (though certainly NOT equivalent to) placebo. There is no obvious dose-related increase in endoscopic ulcers with Cx.***

Clinically significant UGI events

A monitoring program (which included all the arthritis studies : 012, 013, 020, 021, 022, 023, 024, 041, 042, 047, 054, 060, 062, 071, and 087) to identify, review, and confirm all potentially clinically significant UGI events in patients receiving Cx was established. This procedure included an independent Gastrointestinal Consultants Committee consisting of three gastroenterologists who, in a blinded fashion, reviewed case summaries of potentially clinically significant UGI events. For the two pilot studies that began before the monitoring system was established (Studies 012 and 013), patient data were examined retrospectively in an attempt to identify any clinically significant events that may have occurred. Investigators were instructed to immediately report any event considered to represent a potentially clinically significant UGI event (defined as UGI bleeding, perforation, or gastric outlet obstruction). Data pertaining to the event were summarized and distributed in a blinded fashion to each of the Gastrointestinal Consultants to determine whether the event was a clinically significant UGI event.

The committee adjudicated all potentially clinically significant UGI events according to the following prospectively defined criteria:

1. *UGI Bleeding*

- **hematemesis with a lesion* at endoscopy or x-ray,**
- **lesion at endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or clot attached to the base of an ulcer),**
- **melena with a lesion at endoscopy or x-ray,**
- **hemoccult positive stools with a lesion at endoscopy or x-ray with evidence of serious bleeding, which included:**
  - **i. fall in hematocrit over 5% (absolute change)**
  - **ii. signs of postural vital sign changes (increase of pulse rate of 30 bpm and a decrease in systolic blood pressure of 20 mm Hg and a diastolic blood pressure of 10 mm Hg)**
  - **iii. transfusion of more than two units of blood**
  - **iv. blood in the stomach**

*** A lesion is an ulcer or large erosion.**

2. *Perforation*

This was a perforated lesion that required surgery. It could involve a laparoscopic repair, but only if evidence of the perforation were unequivocal such as free air in the abdomen visible by x-ray, or peritoneal signs upon physical examination.

3. *Gastric Outlet Obstruction*

Gastric outlet obstruction was required to be diagnosed by the Investigator, and the diagnosis had to be supported by endoscopy (e.g., a tight edematous ulcer in the pyloric channel) or by x-ray results (e.g., a dilated stomach, delayed barium emptying with clinical evidence of outlet obstruction and with ulcer in the channel or severe narrowing and edema).

The definitions of clinically significant UGI events were based in large part on the design and results of a large prospective study on incidences of clinically significant UGI events caused by NSAIDs.

A total of 170 potential cases (101 in controlled trials, 69 in open-label trial) were reported and evaluated in the celecoxib program. Eighteen (10.6%) of these were judged to have been clinically significant UGI events. Eleven of these occurred in the controlled arthritis trials (as listed above) and seven occurred in the long-term open label trial.

Reviewer's comment: For the interested reader, these events are discussed in great detail in the GI consultant review on UGI safety.

Table 23 below shows the disposition of all potentially clinically significant events in controlled arthritis trials. A total of 101 cases were referred to the Committee for Adjudication. Ninety of these cases were judged not to represent a clinically significant event (the diagnoses for these are listed in the table). Eleven of these met the criteria for clinically significant events.

Table 23. Potential Clinically Significant Events: Controlled Arthritis Trials

	NSAIDs	*Celecoxib*	*Placebo*
Potential events	54	37	10
Not meeting definition of an event	45	35	10
Colonic polyps, colitis, carcinoma, volvulus	2	3	1
Lower GI obstruction, perforation, infarction	0	3	2
Hemorrhoids or rectal disorder	1	0	0
Gastritis/duodenitis/gastroduodenitis	3	3	0
Esophagitis/esophageal ulcer	2	1	0
Uncomplicated gastric ulcer	11	6	0
Uncomplicated duodenal ulcer	6	4	0
Dyspepsia, GE reflux, GERD, hiatal hernia	1	1	1
Pancreatitis, cholelithiasis (or both)	1	1	0
Undetermined diagnosis	18	13	6
Anemia/decreased hematocrit	5	7	1
Blood in stool/black stool/hem-positive stool/melena	1	2	2
Change in bowel habits/diarrhea/ constipation/flatulence	1	3	0
Bright red blood per rectum/hematochezia	2	0	3
Gastric erosions	1	0	0
Intra-abdominal pain	6	0	0
Nausea	1	0	0
Abdominal abscess	0	1	0
Probable laboratory error	1	0	0
Definite Events	9	2	0

The eleven (11) cases judged to represent clinically significant UGI events are summarized further by event type and treatment group in table 24.

Table 24. Definite Clinically Significant UGI Events: Controlled Arthritis Trials

	Placebo	Celecoxib	Naproxen 500 mg BID	Diclofenac 50-75 mg BID	Ibuprofen 800 mg TID
-Hematemesis with lesion	-	-	-	-	-
-Lesion with evidence of active bleeding or stigmata of recent hemorrhage	-	1*	1	2	1
-Melena with a lesion -- Hemoccult (+) stool with a lesion and a decrease in hematocrit of > 5%	-	- 1#	1 1	1 -	- -
-Hemoccult (+) stool with a lesion and signs of postural hypotension	-	-	-	-	-
-Hemoccult (+) stool with a lesion and the need for 2 units of blood	-	-	-	-	-
-Hemoccult (+) stool with a lesion and blood in the stomach	-	-	-	-	-
Perforated ulcer	-	-	-	-	-
Gastric outlet obstruction	-	-	2	-	-
Total	0	2	5	3	1

* = Celecoxib 200 mg BID # = Celecoxib 100 mg BID

As can be seen in table 24, nine events were UGI bleeding episodes occurring in two celecoxib patients, three naproxen patients, three diclofenac patients, and one ibuprofen patient. The other two events were gastric outlet obstructions, both occurring in patients receiving naproxen. No UGI ulcer perforations were judged to have occurred. The two events in celecoxib patients occurred after 14 and 22 days of treatment; events in patients receiving the comparator NSAIDs occurred in a range of one to 61 days after beginning treatment.

The characterization of clinically significant UGI events among treatment groups as a function of length of exposure are shown in table below.

Table 25. Rates of Clinically Significant Events: Controlled Trials

	Placebo	Celecoxib	Naproxen	Diclofenac	Ibuprofen
No. of events	0	2	5	3	1
Patient-years of exposure	208	1020	236	237	62
Annual incidence	0%	0.2%	2.1%	1.3%	1.6%

Although the numbers in all groups are small, it is noteworthy that the ranking of incidences among the groups mirrors the ranking of ulcer incidences noted with the endoscopic studies. The highest incidences were seen for naproxen, followed in descending order by ibuprofen, diclofenac, and then celecoxib and placebo. It should be noted that displaying data from trials that were all less than one year in duration as annual incidence rates is not universally accepted as the most appropriate way to compare this data.

Reviewer's comment: Because of considerations such as the small number of events noted, no valid statistical inferences can be drawn from the data on these clinical endpoints. However, the trends again seem to support the idea that Celecoxib is different than comparator NSAIDs but it is NOT the same (or equivalent) to placebo.

A total of 69 cases in the long-term open label trial (024) were referred to the Committee for evaluation. Sixty-two of these were judged not to clinically significant UGI events. These results will be summarized later in the 120-Day Safety Update. The diagnoses in these seven cases that met the criteria for clinically significant events are noted in table 26 below. (The information discussed in this section represents only those cases with onset on or before the database cutoff date of November 21, 1997.)

Table 26. Definite Clinically Significant UGI Events: Open-Label Trial

	Celecoxib (mg, BID)			
	100	200	300	400
Perforated ulcer	-	-	-	-
Gastric outlet obstruction	-	-	-	-
Hematemesis with a lesion	-	-	-	1
Lesion with evidence of active bleeding or recent hemorrhage	-	1	-	1
Melena with a lesion	1	1	1	1
Hemoccult-(+) stool with lesion and decrease in hematocrit of >5%	-	-	-	-
Hemoccult (+) stool with a lesion and signs of postural hypotension	-	-	-	-
Hemoccult (+) stool with lesion and need for 2 units of blood	-	-	-	-
Hemoccult (+) stool with a lesion and blood in the stomach	-	-	-	-
Total	1	2	1	3

Analysis of the data confirmed that none of the clinically significant UGI events occurred within 90 days of enrollment in a patient who had previously received Naproxen without undergoing an end-of-study endoscopy. This was a concern about carry over of events from this treatment group to that of Cx. Four of the potential events that were evaluated by the Committee did occur in such patients, but none of these met the definition of a significant event. All other potential events evaluated by the Committee occurred in patients who had received Cx or placebo in a previous study, or who had undergone an end-of-treatment endoscopy and therefore were confirmed to be free of ulcers. As can be seen in the table above, all seven UGI events were bleeding events. There were no gastric outlet obstructions or UGI ulcer perforations. These events occurred after a range of 26 to 181 days of treatment.

It is noted that if the seven events shown above are annualized, they represent a rate of clinically significant GI events of 0.26% per year. This is compatible with the rate of 0.2% per patient-year noted in the controlled trials. These results lend further support to the idea that endoscopy-detected ulcers are valid surrogate markers for actual clinical events that require treatment. It would therefore be expected that if the incidence of ulcers is decreased as the ulcer data above show, the incidence of clinically significant UGI events would be similarly decreased.

In the **120-Day Safety Update,** since the ISS was written, the Gastrointestinal Consultants Committee evaluated a total of 45 potential cases from Study 024, representing all cases with an onset between November 22, 1997 and July 24, 1998. Two of these cases were judged to be clinically significant.

> ***Reviewer's comment: An additional case that was judged to represent a clinically significant UGI event occurred after the database cutoff date. A 53-year-old woman (patient 024-US0014-0140024) experienced a perforated duodenal ulcer on August 8, 1998. Therefore, this makes a total of 10 cases as of this writing.***

These two events have been added to the seven identified in the ISS, for a cumulative total of nine clinically significant UGI events for the long-term open-label study. Table 27 below shows the disposition of all these potentially clinically significant UGI events in the long-term, open-label trial.

Table 27. Potential Clinically Significant Events: 120-Day Safety Update

Potential Events	No. of Patients through 11/21/97 (ISS)	No. of Patients through 7/24/98 (ISS + SU)
Not meeting definition of event	69	114
Diverticulosis/diverticulitis/diverticular disease	62	105
Colonic polyps, colitis, carcinoma, volvulus	2	4
Lower GI obstruction, perforation, infarction	5	12
Hemorrhoids or rectal disorder	3	6
Gastritis/duodenitis/gastroduodenitis	2	6
Esophagitis/esophageal ulcer	6	8
Uncomplicated gastric ulcer/pyloric channel ulcer	2	5
Uncomplicated duodenal ulcer	7	11
Dyspepsia, GE reflux, GERD, hiatal hernia	3	3
Cholecystitis, pancreatitis or cholelithiasis (or combination of these)	4	7
Gastric cancer	1	2
Ileus	0	1
Primary/secondary liver cancer	0	1
Undetermined diagnosis	0	1
Anemia/decreased hematocrit	27	38
Blood in stool/black stool/hemoccult-positive stool/melena	6	10
Change in bowel habits/diarrhea/constipation/ flatulence	7	7
BRBPR/hematochezia	2	2
Abdominal pain	2	2
Nausea/vomiting/indigestion	8	12
Epistaxis	0	2
Esophageal stricture secondary to food impaction	1	1
No GI disease	1	1
Definite events	0	1
	7	9

A total of 114 cases were referred to the Committee for evaluation: 69 cases were included in the ISS, and 45 cases were identified with onset of signs or symptoms between November 22, 1997 and July 24, 1998. One hundred five of these were judged not to be clinically significant UGI events. Nine cases met the criteria for clinically significant events: seven were reported in the ISS, and two are newly reported in the 120-Day Update.

These nine cases of definite clinically significant UGI events are summarized by event type and Cx dosage in table 28 below. Interestingly, all nine were UGI bleeding events which occurred after a range of 26 to 434 days of treatment. The two new events were "hematemesis with a lesion" and "lesion with evidence of active bleeding or stigmata of recent hemorrhage".

Table 28. Definite Clinically Significant UGI Events: 120-Day Safety Update

	Celecoxib 100 mg BID (844.1 pt-years)	Celecoxib 200 mg BID (2520.1 pt-years)	Celecoxib 300 mg BID (599.5 pt-years)	Celecoxib 400 mg BID (960.0 pt-years)
Perforated ulcer	-	-	-	-
Gastric outlet obstruction	-	-	-	-
Hematemesis with a lesion	-	-	-	2
Lesion with evidence of active bleeding or stigmata of recent hemorrhage	-	2	-	1
Melena with a lesion	1	1	1	1
Hemoccult-positive stool with a lesion and a decrease in hematocrit of >5%	-	-	-	-
Hemoccult-positive stool with a lesion and signs of postural hypotension	-	-	-	-
Hemoccult-positive stool with a lesion and the need for 2 units of blood transfused	-	-	-	-
Hemoccult-positive stool with a lesion and blood in the stomach	-	-	-	-
Total	1	3	1	4

The rates of clinically significant UGI events in the long-term, open-label study as of the ISS and as of the Safety Update are presented in table 29. It is of interest to note that the rate of 0.18% per patient-year in trial 024 (rate with additional tenth case is 0.2%) is compatible with the rate of 0.2% per patient-year observed in the controlled arthritis trials.

Table 29. Rates of Clinically Significant UGI Events: 120-Day Safety Update

	Through 11/21/97 (ISS)	Through 7/24/98 (SU)
Number of definite events	7	9
Number of patient-years of exposure	2672.4	5001.9
Events per 100 patient-years	0.26	0.18

Derived from ISS Table 4.3 and Safety Update Table 4.2.

Reviewer's comment: The correlation between how well these endoscopic and clinically-relevant events of celecoxib compare, in a statistically meaningful way, to comparator NSAIDs would be addressed more appropriately in a "large and simple" trial (s) designed specifically for this purpose.

Finally, it is of interest to make a comparison of decreases in hematocrit and hemoglobin as noted in the contingency table (Table 30) below:

Table 30. Hematocrit (Hct) by Hemoglobin (Hb-g/dL) Contingency Table[1]

Increase of:	Percent of Patients: Controlled Trials[2] (n=number)			Open-Label
	Cx (6127)	Active Control (2639)	Plc (1756)	Cx (4329)
Hct (≥5%:<10%) and Hb (≥1:≤2)	4.6	8.3	2.8	8.4
Hct ≥10% and Hb > 2	0.3	0.6	0.2	0.4

1.) **Data from Table 1.1 (N49-98-17-819)**
2.) **Includes studies 012, 013, 020, 021, 022, 023, 041, 042, 047, 054, 060, 062, 071 and 087.**

In summary (see UGI Safety Review for details), the results of these GI trials can be summarized as follows:

- **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.**

- **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.**

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

- **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.**

- **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.**

- **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.**