

Celebrex Capsules
(Celecoxib)

NDA 20-998/S-009

Medical Officer Review

Submission Date: June 12, 2000
Received Date: June 14, 2000
Review Date: September 20, 2000

Drug Name: Celebrex™
Generic Name: celecoxib
Chemical Name: 4-[5-(4-methylphenyl)-3-trifluoromethyl]-1H-pyrazol-1-yl] benzenesulfonamide

Applicant: G.D. Searle & Co.

Related Reviews: Statistics, Cardio-Renal, Gastrointestinal (HFD-550)

Pharmacologic category: COX-2 inhibitor

Proposed Indication: Label changes
-Warnings (Clinically Significant UGI Events)

Dosage forms and route: Oral capsule, 100 and 200 mg

Submission type: Supplemental NDA

Materials Reviewed: Primary-document N49-00-06-035_102

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

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

CLASS Executive Summary

Significant Issues/Highlights

- The Celecoxib Long-term Arthritis Safety Study (CLASS) represented the combination of two large safety studies (protocols N49-98-02-035 and N49-98-02-102) which addressed primarily the UGI clinical outcomes of celecoxib, a COX-2 selective agent, as compared to more traditional NSAIDs. In particular, the incidence of clinically significant UGI events (CSUGIEs) associated with celecoxib was compared to that associated with ibuprofen or diclofenac during chronic administration in patients with OA or RA. Patients were allowed to take aspirin (ASA) for cardiovascular prophylaxis. The term “CSUGIE” represented a composite end point comprised of UGI bleeding, perforation, or gastric outlet obstruction. Those symptomatic UGI events deemed not to be CSUGIEs, were referred to as gastroduodenal ulcers (GDU).
- Data in the CLASS trial included information on serum bicarbonates and other estimates of potential effects on acid-base balance. This new data represented a fulfillment of a phase 4 commitment to study these issues since serum bicarbonates had not been measured in the original NDA.
- Overall, the CLASS trial represented a robust test of the safety of celecoxib as compared to the “traditional” NSAIDs of ibuprofen and diclofenac. The latter two compounds were at their “usual” therapeutic doses while celecoxib was given at a “2X” dose which represent twice the currently approved dosing for rheumatoid arthritis. This supratherapeutic dose is the also the currently recommended dose for the labeled indication of familial adenomatous polyposis (FAP).
- Celecoxib did not demonstrate statistical superiority to NSAIDs (pooled) or either comparator (diclofenac and ibuprofen) with regards to the primary safety endpoint of CSUGIEs at any point in the trial although there were trends (noted below) that favored celecoxib. When the subgroup of non-aspirin users was considered, or the definition of the UGI endpoints was expanded to include ulcer events not deemed to be CSUGIEs (i.e. GDUs), celecoxib did demonstrate superiority to pooled NSAIDs, and to ibuprofen (only), during this trial. This superiority was not a pre-specified efficacy endpoint and was not corrected statistically for multiplicity. Celecoxib did not demonstrate statistical superiority to diclofenac regardless of selection of study endpoint or aspirin use during any point in the trial.
- Aspirin use appears to influence event rates for gastrointestinal, renal and possibly cardiac outcomes. However, owing to the nature of this trial, particularly that use of aspirin would indicate a higher level of pre-existing cardiovascular disease and aspirin use was not stratified, it is unclear how aspirin impacts these outcomes among the treatment groups evaluated in this trial.
- The CLASS trial data do not support an apparent adverse effect of celecoxib on cardiovascular mortality or on serious adverse events related to thrombosis relative to either diclofenac or ibuprofen. The data do not exclude a less apparent effect, reflected in the relative rates of cardiac adverse events related to ischemia.
- The CLASS trial data do not support an apparent adverse effect of celecoxib on renal or cardiac adverse events relative to either diclofenac or ibuprofen. This includes adverse events reported by investigators (*e.g.*, hypertension, uremia) and those detected through routine laboratory or blood pressure measurements (*e.g.*, increased BUN/ serum creatinine or systolic blood pressure).

- Overall safety, as defined by the endpoints of deaths, serious adverse events and withdrawals due to adverse events did not appear to be meaningfully or consistently different among the three treatment groups.

Clinical Background (Section 6):

Relevant Human Experience (Section 6.1):

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat chronic arthritic diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA). An important mechanism through which these agents are thought to act is via inhibition of the enzyme cyclooxygenase (COX). This enzyme is now known to exist in two isoforms: a mostly constitutive form (COX-1) and a mostly inducible form (COX-2). However, it is now appreciated that COX-2 can also be constitutively expressed in certain areas in the body. COX-1 is thought to be widely distributed throughout most body tissues and mediates synthesis of prostaglandins that have a diverse array of homeostatic physiological functions. One of these important functions is thought to include the maintenance of mucosal integrity in the upper gastrointestinal (UGI) tract. In contrast, COX-2 in most areas of the body, is thought to be expressed in low levels in tissues but is rapidly and highly induced at sites of inflammation.

Since “traditional” NSAIDs nonspecifically inhibit both COX isoforms, it has been postulated that their anti-inflammatory and analgesic benefits result from inhibition of COX-2 while the increased rate of UGI ulcers and complications commonly associated with NSAIDs result from inhibition of COX-1. The principal manifestations of ulcer complications are UGI bleeding, perforation, and gastric outlet obstruction. The UGI toxicity of NSAIDs has been well documented. For example, observational analysis of the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) database suggests that in a large population receiving NSAIDs over 10,600 patient-years, GI-related hospitalizations or deaths occurred at a rate of 1.3% per year. Most studies in this area, such as the one cited, have been observational cohort or retrospective case-control studies. In the only large, randomized, prospective trial of NSAID-related UGI ulcer complications (the MUCOSA trial), the annualized incidence was approximately 1.9% in 8843 RA patients followed for six months; the risk of UGI ulcer complications did not seem to diminish with continuing exposure.

This risk of UGI complications noted for NSAIDs resulted in the formation of a GI paragraph which has been included in the labeling of approved NSAIDs. The current labeling for Celebrex is as follows:

WARNINGS

Gastrointestinal (GI) Effects- Risk of GI Ulceration, Bleeding, and Perforation:

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated

with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

It is unclear, at the present time, how the above rates apply to CELEBREX. (See CLINICAL STUDIES-Special Studies.) Among 5285 patients who received CELEBREX in studies of 1 to 6 months duration, at a daily dose of 200 mg or more in controlled clinical trials, 2 (0.04%) experienced significant upper GI bleeding at 14 and 22 days after initiation of dosing. Approximately 40% of these 5285 patients were in studies that required them to be free of ulcers by endoscopy at study entry. (Thus this study population may have been at lower risk for significant gastrointestinal complications.) **Thus it is unclear if this study is representative of the general population.** Prospective, long-term studies required to compare the occurrence of serious clinically significant upper GI adverse events in patients taking CELEBREX vs. comparator NSAID products have not been performed.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding and who use NSAIDs, have a greater than 10-fold **higher** risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

An important hypothesis for development of selective inhibitors of COX-2 has been that they, by avoiding inhibition of COX-1, would spare the UGI tract toxicity while maintaining analgesic and anti-inflammatory efficacy. A corollary to this has been the impression that COX-2 agents may also be safer, overall, as compared to traditional NSAIDs. The original NDA for Celebrex included data on endoscopically-defined UGI endpoints, but insufficient data on clinical UGI outcomes to allow for any substantial modification of the GI Warning paragraph. **This sNDA, which consists basically of two large safety studies (protocols N49-98-02-035 and N49-98-02-102), seeks to address primarily the UGI clinical outcomes of celecoxib, a COX-2 selective agent, as compared to more traditional NSAIDs.** In particular, the incidence of clinically significant UGI events (CSUGIEs) associated with celecoxib was compared to that associated with ibuprofen or diclofenac during chronic administration (at least six months) in patients with OA or RA. The term "CSUGIE" represents a composite end point comprised of UGI bleeding, perforation, or gastric outlet obstruction. It should be noted that these companion protocols were prospectively designed with the intent to

combine the results into a single study, pooling the celecoxib patients from both protocols into a single treatment group.

Safety evaluation:

All patients who took at least one dose of study medication were included in all safety analyses. Adverse events (AE) were coded using W.H.O.a.r.t. terminology. The incidences of treatment-emergent adverse events were tabulated by treatment group and body system, and compared pairwise between treatment groups using Fisher's Exact test. Events occurring more than 28 days after the last dose of study medication were excluded from all analyses.

Adverse events causing withdrawal were similarly analyzed. Serious adverse events were tabulated by treatment group and body system, but no statistical analysis was performed. The incidences of treatment-emergent adverse events were also tabulated by severity and by the Investigator's attribution of the cause of the event.

Because of the long treatment period in this study, a separate analysis was performed in which adverse events were summarized by 90-day intervals (1 to 90 days, 91 to 180 days, 181 to 270 days, 271 to 360 days, 361 to 450 days, and 451 to 540 days). In this analysis, incidences and prevalences were summarized separately for each adverse event. Within each interval, events were counted under prevalence if they were new in that interval or continued from a previous interval, whereas incidence values included only events that were new within that interval.

For selected GI adverse events, time-to-event analyses were performed to assess the rates of the events by pre-specified time intervals (1, 4, 13, 26, 39, 52, and 65 weeks). The log-rank test was used to compare the time-to-event curves between celecoxib 400 mg BID and the two NSAIDs combined, as well as between celecoxib and each of the NSAIDs separately. Each test was performed at the alpha level of 0.05.

Times to withdrawal due to adverse events were analyzed using the log-rank test. In this analysis, patients who withdrew for other reasons were censored at the time of withdrawal; those who did not withdraw at any time were censored at the final scheduled visit.

Changes from baseline in clinical laboratory values at weeks 4, 13, 26, 39, 52, and the final visit were summarized as means and standard deviations (SD). The changes were compared among treatment groups by ANCOVA using pairwise treatment contrasts with baseline value as the covariate.

Incidences of extreme laboratory (and vital signs) values during the study were summarized by treatment group and compared among groups using Fisher's exact test. The values representing upper and lower extremes for each laboratory test were determined before the initiation of study conduct through discussions with external safety consultants, and were listed (Table 6.d, N49-00-06-035-102, p. 52/24295) and were utilized to construct shift tables. Contingency tables were also prepared showing numbers

of patients whose post-treatment laboratory results met certain criteria for combinations of values or changes in values that might indicate hematologic, hepatobiliary, or renal effects. These criteria represented: decreases in both hemoglobin and hematocrit; increases in both creatinine and BUN; increases in both AST and ALT; increases in both alkaline phosphatase and total bilirubin; increases in both ALT and alkaline phosphatase; and increases in both ALT and total bilirubin. These tables showed numbers of patients shifting among various categories of increases and decreases according to predetermined cutoff values.

Other Serious Adverse Events:

A total of 500 patients experienced **serious adverse events (SAE)** during or 28 days after study participation:

- 270 patients in the celecoxib group
- 111 patients in the diclofenac group
- 119 patients in the ibuprofen group

The most common SAEs are summarized in **Table 41**. As can be seen, the difference between any two treatment groups was no more than 0.6 per 100 patient-years. The highest rate seen for any serious adverse event was 0.8 per 100 patient-years, seen in at least one treatment group for myocardial infarction, coronary artery disorder, accidental fracture, cardiac failure, and back pain. Although the results are similar to those shown for general adverse events, the patterns suggested by the general adverse events were not replicated exactly in the serious adverse events. This difference in pattern may reflect the fact that there were smaller numbers of serious events than general adverse events.

Table 41: Summary of Serious Adverse Events-Entire Study Period¹

Adverse Event	Celecoxib (n=3987) 2320.4 pt-yrs	Diclofenac (n=1996) 1080.5 pt-yrs	Ibuprofen (n=1985) 1122.5 pt-yrs
Any serious event	270 (11.6)	111 (10.3)	119 (10.6)
Abdominal pain	6 (0.3)	6 (0.6)	2 (0.2)
Accidental fracture	10 (0.4)	4 (0.4)	9 (0.8)
Accidental injury	3 (0.1)	4 (0.4)	7 (0.6)
Angina pectoris	4 (0.2)	5 (0.5)	6 (0.5)
Atrial fibrillation	9 (0.4)	2 (0.2)	3 (0.3)
Back pain	15 (0.6)	3 (0.3)	9 (0.8)
Cardiac failure	9 (0.4)	2 (0.2)	9 (0.8)
Cellulitis	8 (0.3)	1 (<0.1)	1 (<0.1)
Cerebrovascular disorder	4 (0.2)	6 (0.6)	6 (0.5)
Chest pain	11 (0.5)	5 (0.5)	7 (0.6)
Coronary artery disorder	19 (0.8)	5 (0.5)	5 (0.4)
Deep thrombophlebitis	7 (0.3)	5 (0.5)	1 (<0.1)
GI hemorrhage	7 (0.3)	2 (0.2)	1 (<0.1)
Myocardial infarction	19 (0.8)	4 (0.4)	9 (0.8)
Pneumonia	14 (0.6)	5 (0.5)	5 (0.4)
Syncope	5 (0.2)	4 (0.4)	3 (0.3)
Unstable angina	8 (0.3)	4 (0.4)	0

- 1 From Table 10.g (p 184); N49-00-06-035-102. Owing primarily to the unequal randomization, results are displayed as normalized for length of exposure, rather than crude incidence rates. Table includes any event experienced by a total of at least 10 patients across the three treatment groups.

Reviewer's comment: Generally, these normalized incidences do not seem to suggest any important differences or obvious trends of specific target organ or organ-system involvement by any treatment group.

Renal Effects

Table 50 shows the incidences of selected renal adverse events occurring throughout the entire study period. In general, the incidences were low in all treatment groups, not suggesting any pronounced renal effects of any of these treatments. However, patients receiving ibuprofen experienced more edema and hypertension than celecoxib or diclofenac patients; these differences were statistically significant. Adverse events relating to increases in renal function laboratory values (BUN increased and NPN increased) were more frequent for diclofenac than for celecoxib. The differences were statistically significant when examined in the six-month analysis, but not over the entire treatment period.

Table 50: Selected Adverse Events Relating to Renal Function: Entire Study Period¹

Adverse Event	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
Hypertension	2.0	2.0	3.1*
Hypertension aggravated	0.8	0.6	1.2
Edema generalized	0.5	0.6	1.0*
Edema peripheral	3.7	3.5	5.2 *
Cardiac failure	0.3	0.2	0.5
BUN increased	1.1	1.7	0.9
NPN increased	1.3	1.9	1.2
Renal failure acute	0.0	<0.1	0.0
Renal function abnormal	<0.1	<0.1	0.1

1. From Table 10.q (p 201); N49-00-06-035-102. All numbers are percentages of patients. (*) =p<0.05 vs. celecoxib.

Reviewer's comment: For a more detailed analysis of the cardiovascular and renal effects of celecoxib and the comparator groups in this trial, the reader is referred to the review by Douglas Throckmorton, M.D.

Table 51 shows group mean changes and extreme changes in BUN and creatinine. Although the meaning is unclear, the results suggest an effect of diclofenac on mean creatinine values, and of celecoxib on BUN as compared to ibuprofen. Few patients experienced an extreme BUN value; the incidence appeared higher for ibuprofen than for the other two groups, but the difference was not statistically significant. When the extreme creatinine threshold of 265 µmol/L was used, only one patient in the entire study period experienced an extreme value. However, as noted above for the renal contingency tables, when the lower threshold of 159 µmol/L for creatinine with or without BUN changes was utilized, percent increases of 1.3 for celecoxib, 2.1 for diclofenac, and 1.4

for ibuprofen were noted. The difference between celecoxib and diclofenac was statistically significant.

Not shown in Table 51 was that between celecoxib and ibuprofen in elevated potassium levels: 0.3% of celecoxib patients and 0.0% of ibuprofen patients had a maximum potassium value above 6.0 mmol/L (p=0.021; Table 45.1,p. 535). Five of these 11 cases of extreme potassium levels in celecoxib patients were isolated increases that were bracketed by values within the normal range, and may be artifactual (i.e., due to hemolysis). One additional case was an isolated value drawn four days after discontinuation of study medication and is of uncertain clinical significance.

Table 51: Mean Changes from Baseline to Final Visit/Extreme Values in Specific Renal Laboratory Values¹

Laboratory Test	Celecoxib	Diclofenac	Ibuprofen
Group Mean Changes from Baseline (Mean [SE])			
BUN, mmol/L	0.66 (0.027)	0.58 (0.041)	0.52 (0.039) ¹
Creatinine, μmol/L	0.8 (0.22)	2.4 (0.33) ¹	1.5 (0.33)
Incidence of Extreme Values (No./total [%])			
BUN (>14.3 mmol/L)			
Final visit	17/3692 (0.5)	8/1849 (0.4)	12/1786 (0.7)
Maximum value	31/3692 (0.8)	20/1849 (1.1)	16/1786 (0.9)
Creatinine (>265.2 μmol/L)			
Final visit	0/3692 (0.0)	0/1850 (0.0)	0/1786 (0.0)
Maximum value	1/3692 (<0.1)	0/1850 (0.0)	0/1786 (0.0)

1. From Table 10.r (p 202); N49-00-06-035-102. P<0.05 vs. celecoxib.

Vascular (Cardiac and Noncardiac) Effects

The incidences of cardiac and noncardiac vascular adverse events throughout the entire study period are shown in Table 52. The table shows that vascular events were rare in all treatment groups, and incidences were similar between celecoxib and the two NSAIDs. The only statistically significant difference in incidences was for cerebrovascular disorder between celecoxib (0.2%) and ibuprofen (0.5%).

Table 52: Incidences of Selected Cardiac/Noncardiac Vascular Adverse Events: Entire Study Period¹

Adverse Event	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
Angina pectoris	0.6	0.5	0.6
Arteriosclerosis	<0.1	0.0	<0.1
Atherosclerosis	<0.1	<0.1	0.1
Carotid bruit	<0.1	0.1	<0.1
Carotid stenosis	<0.1	0.0	0.0
Cerebrovascular disorder	0.2	0.5	0.5 ¹
Coronary artery disorder	0.6	0.4	0.3
Embolism	<0.1	0.0	0.0
Embolism pulmonary	0.1	<0.1	0.1
Myocardial infarction	0.5	0.3	0.5
Myocardial ischemia	<0.1	0.1	0.0
Peripheral gangrene	<0.1	0.0	0.0

Peripheral ischemia	0.1	0.0	0.1
Peripheral vascular disease	<0.1	0.0	<0.1
Phlebitis	<0.1	0.0	<0.1
Thrombophlebitis	<0.1	0.0	<0.1
Thrombophlebitis arm	<0.1	0.0	<0.1
Thrombophlebitis deep	0.3	0.3	<0.1
Thrombophlebitis leg	0.0	<0.1	<0.1
Thrombophlebitis leg deep	<0.1	<0.1	0.0
Thrombophlebitis leg superficial	<0.1	<0.1	0.0
Unstable angina	0.3	0.2	0.1

1. From Table 10.s (p 204); N49-00-06-035-102. Numbers are percentages. P<0.05 vs. celecoxib.

Reviewer's comment: There does not appear to be any clinically or statistically significant trend with celecoxib to suggest additional cardiovascular risks over the comparator drugs.

Incidences of the same group of adverse events are shown and statistically analyzed by aspirin status in **Table 53**. Patients in the two NSAID groups were pooled for this analysis. As might be expected, incidences of the cardiovascular-related events were higher in the patients taking aspirin, since these patients were more likely to have a significant cardiovascular medical history than the overall study population. The absence of statistical significance for any of the events suggest that the differences between celecoxib and NSAID were not markedly altered by the use of aspirin.

Table 53: Incidences of Selected Cardiac/Noncardiac Vascular Adverse Events with/without Aspirin Use: Entire Study¹

	With Aspirin			Without Aspirin		
	Celecoxib (n=882)	NSAIDs (n=857)	RD*	Celecoxib (n=3105)	NSAIDs (n=3124)	RD*
Any thromboembolic event	6.1	5.7	0.4	1.5	1.2	0.3
Angina pectoris	1.5	1.6	-0.2	0.3	0.3	0.0
Arteriosclerosis	0.2	0.1	-	0.0	0.0	-
Atherosclerosis	0.1	0.2	-0.1	<0.1	<0.1	0.0
Carotid bruit	0.0	0.1	-0.1	<0.1	<0.1	0.0
Carotid stenosis	0.1	0.0	-	0.0	0.0	-
Cerebrovascular disorder	0.6	1.2	-0.6	<0.1	0.3	-0.2
Coronary artery disorder	1.7	0.9	0.8	0.3	0.2	0.2
Embolism	0.0	0.0	-	<0.1	0.0	-
Embolism pulmonary	0.1	0.0	0.1	<0.1	<0.1	0.0
Myocardial infarction	1.5	1.2	0.3	0.2	0.1	0.1
Myocardial ischemia	0.1	0.2	-0.1	<0.1	0.0	0.0
Peripheral gangrene	0.0	0.0	-	<0.1	0.0	-
Peripheral ischemia	0.3	0.1	0.2	<0.1	<0.1	0.0
Peripheral vascular disease	0.1	0.0	0.1	<0.1	<0.1	0.0
Phlebitis	0.0	0.0	-	<0.1	<0.1	-
Thrombophlebitis	0.0	0.0	-	<0.1	<0.1	-
Thrombophlebitis arm	0.0	0.0	-	<0.1	<0.1	-
Thrombophlebitis deep	0.3	0.4	0.0	0.3	<0.1	0.2
Thrombophlebitis leg	0.0	0.0	-	0.0	<0.1	-
Thrombophlebitis leg deep	0.0	0.0	-	<0.1	<0.1	-
Thrombophlebitis leg superficial	0.0	0.1	-0.1	<0.1	0.0	0.0
Unstable angina	0.9	0.6	0.3	<0.1	<0.1	0.0

1. From Table 10.t (p 205); N49-00-06-035-102. Numbers are percentages. RD indicates risk reduction. None of the differences were statistically significant at $p < 0.05$.

Table 54 (from Cardiorenal review, Doug Throckmorton, M.D.) shows selected cardiac adverse events reported during the trial according to aspirin use. For anginal disorders (especially the combined disorders), there seems to be a trend toward more events in those patients receiving celecoxib, regardless of aspirin use. However, for edema, there appears to be a trend toward more events in those patients receiving ibuprofen.

Table 54: Selected Cardiac Adverse Events Reported During CLASS According to ASA Use^a.

Adverse Event	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
<u>ASA-Users</u>	N=882	N=445	N=412
Edema			
Edema peripheral	35 (4.0%)	17 (3.8%)	23 (5.6%)
Edema (pooled reporting) ^b	38 (4.3%)	20 (4.5%)	28 (6.8%)
Angina			
Unstable Angina	8 (0.9%)	4 (0.9%)	1 (0.2%)
Angina Pectoris	13 (1.5%)	8 (1.8%)	6 (1.5%)
Coronary Artery Disorder	15 (1.7%)	3 (0.7%)	5 (1.2%)
Combined Anginal Disorders^c	36 (4.1%)	15 (3.4%)	12 (2.9%)
Myocardial Ischemia	1 (0.1%)	2 (0.4%)	0 (0%)
Myocardial Infarction	13 (1.5%)	3 (0.7%)	7 (1.7%)
Hypertension	24 (2.7%)	14 (3.1%)	19 (4.6%)
Hypertension Aggravated	12 (1.4%)	2 (0.4%)	7 (1.7%)
Thrombophlebitis			
Thrombophlebitis, Deep	3 (0.2%)	2 (0.4%)	1 (0.2%)
Thrombophlebitis, Combined ^d	3 (0.2%)	3 (0.4%)	1 (0.2%)
Vasculitis	1 (0.1%)	0 (0%)	0 (0%)
<u>Non-ASA Users</u>	N=3105	N=1551	N=1573
Edema peripheral	111 (3.6%)	53 (3.4%)	81 (5.1%)
Edema (pooled reporting) ^b	127 (4.1%)	61 (3.9%)	96 (6.1%)
Angina			
Unstable Angina	2 (<0.1%)	0 (0%)	1 (<0.1%)
Angina Pectoris	9 (0.3%)	2 (0.1%)	6 (0.4%)
Coronary Artery Disorder	10 (0.3%)	4 (0.3%)	1 (<0.1%)
Combined Anginal Disorders^c	21 (0.67%)	6 (0.38%)	8 (0.51%)
Myocardial Ischemia	1 (<0.1%)	0 (0%)	0 (0%)
Myocardial Infarction	6 (0.2%)	2 (0.1%)	2 (0.1%)
Hypertension	54 (1.7%)	26 (1.7%)	42 (2.7%)
Hypertension Aggravated	20 (0.6%)	10 (0.6%)	17 (1.1%)

Thrombophlebitis			
Thrombophlebitis, Deep	9 (0.3%)	3 (0.2%)	0 (0%)
Thrombophlebitis, Combined ^d	14 (0.45%)	5 (0.3%)	4 (0.25%)
Vasculitis	1 (<0.1%)	0 (0%)	1 (<0.1%)

1. Data from electronic submission, NDA 20-998 supplement S-009, Table T41.1.

b. Includes edema, edema generalized, and edema peripheral.

c. Includes unstable angina, angina pectoris and coronary artery disorder.

d. Includes AEs reported under the following terms: phlebitis, thrombophlebitis, thrombophlebitis arm, thrombophlebitis deep, thrombophlebitis leg, thrombophlebitis leg deep, thrombophlebitis leg superficial.

Table 55 (from Cardioresenal review, Doug Throckmorton, M.D.) shows serious cardiac adverse events reported during the trial according to aspirin use. In the non-aspirin users, there appears to be a slight trend toward more events in those patients receiving celecoxib for combined atrial and anginal disorders; this does not appear to be the case for aspirin users.

Table 55: Serious Adverse Events (SAEs) per 100 Pt-Yrs Reported During CLASS by ASA Use^a.

Adverse Event	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
ASA Users	N=882 517 Pt-Yrs	N=445 N=239 Pt-Yrs	N=412 249 Pt-Yrs
Cardiac SAEs			
Atrial Arrhythmias			
Arrhythmia Atrial	2 (0.4%)	0 (0%)	1 (0.4%)
Bradycardia	0 (0%)	0 (0%)	0 (0%)
Fibrillation Atrial	4 (0.8%)	1 (0.4%)	3 (1.2%)
Tachycardia Supraventricular	1 (0.2%)	0 (0%)	0 (0%)
Combined Atrial SAEs ^b	7 (1.4%)	1 (0.4%)	4 (1.6%)
Angina			
Unstable Angina	6 (1.2%)	4 (1.7%)	0 (0%)
Angina Pectoris	3 (0.6%)	5 (2.1%)	4 (1.6%)
Coronary Artery Disorder	11 (2.1%)	2 (0.8%)	5 (2.0%)
Combined Anginal Disorders ^c	20 (3.9%)	11 (4.6%)	8 (3.2%)
Myocardial Infarction	13 (2.5%)	2 (0.8%)	7 (2.8%)
Thrombophlebitis Combined ^d	0 (0%)	2 (0.8%)	1 (0.4%)
Non-ASA Users	N=3105 1804 Pt-Yrs	N=1551 841 Pt-Yrs	N=1573 874 Pt-Yrs
Cardiac SAEs			
Atrial Arrhythmias			
Arrhythmia Atrial	0 (0%)	0 (0%)	0 (0%)
Bradycardia	2 (0.1%)	0 (0%)	0 (0%)

Fibrillation Atrial	5 (0.3%)	1 (0.1%)	0 (0%)
Tachycardia Supraventricular	2 (0.1%)	0 (0%)	0 (0%)
Combined Atrial SAEs^b	6 (0.3%)	1 (0.1%)	0 (0%)
Angina			
Unstable Angina	2 (0.1%)	0 (0%)	0 (0%)
Angina Pectoris	1 (<0.1%)	0 (0%)	2 (0.2%)
Coronary Artery Disorder	8 (0.4%)	3 (0.4%)	0 (0%)
Combined Anginal Disorders^c	10 (0.6%)	3 (0.4%)	2 (0.2%)
Myocardial Infarction	6 (0.3%)	2 (0.2%)	2 (0.2%)
Thrombophlebitis Combined ^d	8 (0.4%)	4 (0.5%)	0 (0%)

1. Data from electronic data submission, Appendix 2.9.4 and 2.9.3.

b. Sum of atrial arrhythmia, atrial fibrillation, bradycardia and tachycardia.

c. Includes unstable angina, angina pectoris and coronary artery disorder.

d. Includes AEs reported under the following terms: phlebitis, thrombophlebitis, thrombophlebitis arm, thrombophlebitis deep, thrombophlebitis leg, thrombophlebitis leg deep, thrombophlebitis leg superficial.

e. These SAEs were not reported by investigators.

Discussion/Conclusions (Section 12):

Safety

In contrast to efficacy, the CLASS trial was designed to assess safety endpoints of celecoxib relative to the NSAIDs, diclofenac and ibuprofen. In so doing, arguments were made that this trial was also testing the COX-2 safety hypothesis; this hypothesis being (in general terms) that if COX-2 is not present in any particular organ or cell, drugs targeting COX-2 should not be a problem. Safety may be considered more from the molecular understanding of receptor structure and function, and less so from the prospective of a xenobiotic with its potentially unknown (and non-mechanism based) safety hazards.

The central clinical trial feature in CLASS that tested this hypothesis was the bona fide use of twice to four-fold the highest doses for two FDA-approved labeled indications, RA and OA respectively. As noted by the Sponsor, the multiples of dosing employed for celecoxib was to make comparisons of safety in a “robust” fashion. A safety trial, with “NSAIDs” at similar multiples of their respective labeled doses for OA and RA has not yet been conducted despite the long history of usage of these important and widely used drugs. Unfortunately, the fact that such multiples of the NSAIDs selected for this trial were not included ultimately confounds all discussions and/or conclusions of this CLASS trial.

While some might comment that these multiples were not robust enough (i.e. should be 10X), it appears clear that the dosing, sample size, and selection of safety endpoints all contributed to the highly unique and progressive character of the CLASS trial. Certainly, pushing the envelope in terms of safety has the potential for improvements in safety at both the patient and population levels. As noted, one of the unique aspects of the CLASS trial was the selection of the primary UGI safety endpoint. The gastrointestinal toxicity of NSAIDs, particularly to the upper GI tract, has long been felt by many to be one of the most important iatrogenic adverse events associated with modern drug therapies.

Cardiovascular events

(More details of cardiovascular events are found in the review by Douglas Throckmorton, M.D.)

When considering the deaths and other serious adverse events that occurred in this trial, they appear to be consistent in nature and frequency with those that would be expected in a long-term trial in this patient population. For example, most patients enrolled had several concomitant illnesses or significant medical histories, and many were elderly. As noted (Table 5) the median age was approximately 61 years, with about 11% of patients in each group ≥ 75 years. Approximately 40% of patients in each treatment group had a self-reported history of cardiovascular disease and approximately 20% took ASA prophylactically.

While serious adverse events and deaths related to cardiovascular disorders were not unexpected, was there evidence in the CLASS trial that any treatment group had an excess of these types of events relative to the other groups? For example, concerns have been raised about the possibility that COX-2 selective agents may predispose to thromboembolic events (i.e. myocardial infarction, deep venous thrombosis, pulmonary emboli, cerebrovascular accidents, etc.) owing to their preferential inhibition of endothelial prostacyclins relative to platelet thromboxanes. Further, literature reports of trials (i.e. VIGOR) of other COX-2 selective agents have also raised this possibility.

In the original NDA, myocardial infarction was noted to occur at a higher rate in celecoxib-treated as compared to placebo-treated patients. In the long-term trial (Trial 024) that was included in the NDA submission, the predominate (>90%) cause of death for patients taking celecoxib at any dose was cardiovascular. The majority of these deaths were felt to represent progression of previously known cardiovascular disease. Examination of Kaplan-Meier survival curves for both the controlled and long-term trials in the NDA did not support the conclusion that there was a relationship between any given duration of exposure to celecoxib and increased mortality. There were suggestions of a dose-response relationship (Table 60, NDA 20-998; 100 mg BID celecoxib, 0% crude mortality rate vs. 400 mg BID celecoxib, 0.64% crude mortality rate) between cardiovascular mortality and celecoxib use that could not be adequately addressed by the data. However, the cardiovascular mortality rates with celecoxib were lower than those seen with the active controls employed in the NDA, which confounded interpretation of these data. Of note, there was no suggestion, in the original NDA, of any rare or unusual cardiac toxicities.

In the CLASS trial, it is not possible to examine any dose-response relationships, rather, only comparisons of drugs at the doses employed and in the population studied. Given these caveats, there was no apparent, consistent adverse effect of celecoxib in the reported parameters of cardiovascular safety when compared to either diclofenac or ibuprofen (Table 52). When these events were examined with or without aspirin use, these relationships did not appear to change (Table 53) in any significant way. However, as expected since they are at higher risk, patients taking aspirin had a higher incidence of cardiac ischemic events in all three treatment groups as compared to those not taking

aspirin. Of note, discontinuations for thrombotic cardiac events were not significantly different in the treatment groups (Table T41.1, sNDA and 2.1.d.1, Cardioresenal Consult).

When cardiac adverse events (Table 54) or serious cardiac adverse events (Table 55) and the relationship of **aspirin use** are analyzed in more detail, some differences appear to emerge. For example, examination of selected cardiac adverse events (Table 54) reported during the trial suggests that anginal disorders (especially the combined disorders) was numerically higher in those patients receiving celecoxib, regardless of aspirin use. In the patients not receiving aspirin, the rate of myocardial infarction was also slightly higher in the celecoxib group (0.2%) compared with the other two drugs (0.1%). Of note, for edema and hypertension, there appears to be a trend toward more events in those patients receiving ibuprofen regardless of aspirin use.

For serious cardiac adverse events (Table 55) in the non-aspirin users, there appears to be a trend toward more events in those patients receiving celecoxib for atrial events and anginal disorders, especially when combined; this does not appear to be the case for aspirin users. The importance of any of these differences are difficult to interpret especially since the trial randomization was not stratified for aspirin use, any comparisons of the aspirin or non-aspirin users has limited power to detect only large differences between these groups. This difficulty in interpretation is also evident in considering cardiovascular mortality rates (Table 39 and comment). Overall though, these findings would not seem to support a conclusion that celecoxib has a large adverse effect on cardiovascular mortality compared to the non-selective NSAIDs. If the incidence rates for adverse events (including serious) is confirmed in trials designed to specifically address these important issues, it may be that the degree of loss of blood flow may be a factor in understanding these events, compared to mortality.

Renal events

(More details of renal events are found in the review by Douglas Throckmorton, M.D.)

As noted in the original NDA, the overall findings with celecoxib were that renal events were more like the comparator NSAIDs than the placebo controls. For example, there was an association between celecoxib administration and the development of clinically significant edema (i.e. peripheral), sodium retention, worsened hypertension in susceptible individuals, hypophosphatemia, hyperchloremia, and elevations of serum creatinine and BUN with proteinuria as was noted in the comparator NSAIDs. There were not clear signals, however, for serious renal events such as bony fractures (suggesting significant acid-base changes), renal stone formation, nephrotic syndrome, acute renal failure requiring dialysis, papillary necrosis, or interstitial nephritis. However, there were patients on celecoxib that were withdrawn from the long-term, open-label trial (Trial 024) because of renal adverse events, including acute renal failure. One outstanding issue was whether celecoxib altered the acid-base balance since no measurements (e.g. serum bicarbonate, arterial pH) were performed as part of the original NDA.

Regarding the issue of acid-base balance, serum HCO₃ was measured in the CLASS trial and adverse events possibly related to changes in acid-base balance were collected. Between 1 and 2% of the subjects in all three treatment groups had a measured HCO₃ <20 meq/dl during the study after starting with a normal baseline >25 mg/dl. The rate for celecoxib, however, was less than that of the two comparator drugs. In addition, there was no increase in reported clinical adverse events related to changes in acid-base balance (such as bony fractures which could indicate chronic acidosis with demineralization, Table T41.1, sNDA) in the celecoxib group although such adverse events were quite rare in the database for all three drugs. Overall, then, the rate of clinically-relevant changes in acid-base balance was similar for celecoxib, diclofenac and ibuprofen.

Regarding the comparative incidence of reported clinical renal adverse events between the three treatment groups, there was no consistent adverse effect of celecoxib in the reported parameters of renal safety when compared with either diclofenac or ibuprofen. In particular, the reported rates of uremia, nephrotic syndrome and severe hyperkalemia in CLASS were all less than 1 per 1000 patient-years of exposure for all three drugs. Celecoxib use was also not apparently associated with an increase in hypertension or edema compared with diclofenac and ibuprofen (Table 50).

When renal adverse events related to laboratory measurements were examined, celecoxib did not appear to have a striking adverse effect with regard to any renal parameter measured, compared with diclofenac or ibuprofen (Tables 47, 50). The incidence of hyperkalemia, assessed as clinical events and as changes in lab measurements, was consistently more common in the celecoxib group than in either of the comparators, although the difference did not achieve nominal statistical significance for any measure (Table T 41.1 sNDA and 2.1.c.1 and 2.1.c.2, Cardiorenal Consult).

Regarding changes in renal laboratory parameters, **when examined as mean changes** from baseline, no clinically relevant differences between the three treatment groups were seen at any time point for the changes in mean BUN, serum creatinine, phosphate, bicarbonate and chloride. The reported differences, some of which achieved nominal statistical significance, were quite small and of no apparent clinical relevance (Table T44.1, sNDA). Use or not of aspirin did not seem to influence these particular results.

Of note, it does appear that patients who used **aspirin** in all three treatment groups had a higher incidence of increases in BUN than patients who did not use aspirin. Hyperkalemia as an AE was somewhat higher in the celecoxib group, regardless of aspirin use (Table T 41.2 and T41.3, sNDA and 2.1.c.2, Cardiorenal Consult). For the renal SAEs (Table T43, sNDA and 2.1.b.1, Cardiorenal Consult), too few (i.e. none in any treatment group for hyper- or hypokalemia, acidosis, nephrotic syndrome, edema, uremia-1 case for ibuprofen, or renal calculus-4 cases for celecoxib, 2 for ibuprofen) were reported to analyze according to the use of aspirin.

Overall Safety of Celebrex

The results presented in this sNDA with celecoxib at the supratherapeutic doses studied, support the overall safety of celecoxib. While adverse events for celecoxib during the entire study period were statistically greater than those of the comparator drugs (Table 42), this did not seem to translate into more withdrawals for celecoxib versus ibuprofen

or diclofenac (Table 3). Also, although serious adverse events were numerically higher for celecoxib (Table 41), there were no obvious trends to suggest any specific safety risks. Similarly, the death rate and pattern (Tables 38 and 39) did not suggest any obvious safety risks for celecoxib. Interestingly, no deaths in the celecoxib group occurred for GI, hepatic, renal or dermatologic causes, but the same was true for the comparators.

Conclusions:

As noted earlier, the CLASS trial was a robust testing of the safety of Celebrex at doses 2-4 times those currently labeled for RA or OA, respectively. The NSAID comparators, ibuprofen and diclofenac, were given at their commonly prescribed (not maximum) doses. Therefore, any conclusions regarding the relative safety or efficacy of Celebrex needs to be viewed in this context. However, the following are some conclusions from this CLASS trial:

1. Celecoxib does not appear to be more effective for treating the signs and symptoms of OA or RA than the NSAID comparators.
2. Celecoxib did not demonstrate statistical superiority to NSAIDs (pooled) or either comparator (diclofenac and ibuprofen) with regards to the primary safety endpoint of CSUGIEs at any point in the trial although there were trends (noted below) that favored celecoxib. When the subgroup of non-aspirin users was considered, or the definition of the UGI endpoints was expanded to include ulcer events not deemed to be CSUGIEs (i.e. GDUs), celecoxib did demonstrate superiority to pooled NSAIDs, and to ibuprofen (only), during this trial. This superiority was not a pre-specified efficacy endpoint and was not corrected statistically for multiplicity. Celecoxib did not demonstrate statistical superiority to diclofenac regardless of selection of study endpoint or aspirin use during any point in the trial.
3. Aspirin use appears to influence event rates for gastrointestinal, renal and possibly cardiac outcomes. However, owing to the nature of this trial, particularly that use of aspirin would indicate a higher level of pre-existing cardiovascular disease and aspirin use was not stratified, it is unclear how aspirin impacts these outcomes among the treatment groups evaluated in this trial.
4. Of note, a “paradoxical” effect was noted with regards to ASA use and the UGI endpoints of CSUGIE \pm GDU. While co-use of ASA increased rates of these events in the celecoxib and diclofenac arms, the events decreased in the ibuprofen arm. The clinical significance, if any, of these results remains to be determined from the database.
5. The CLASS trial contains no evidence for an adverse effect of celecoxib on acid-base balance relative to either diclofenac or ibuprofen. All groups rarely had changes in this renal parameter.

6. The CLASS trial data do not support an apparent adverse effect of celecoxib on cardiovascular mortality or on serious adverse events related to thrombosis relative to either diclofenac or ibuprofen. The data do not exclude a less apparent effect, reflected in the relative rates of cardiac adverse events related to ischemia.
7. The CLASS trial data do not support an apparent adverse effect of celecoxib on renal or cardiac adverse events relative to either diclofenac or ibuprofen. This includes adverse events reported by investigators (*e.g.*, hypertension, uremia) and those detected through routine laboratory or blood pressure measurements (*e.g.*, increased BUN/ serum creatinine or systolic blood pressure).
8. Hyperkalemia, however measured, was consistently more frequent in patients taking celecoxib than for diclofenac or ibuprofen, but these differences were small and not reflected in an increase in serious adverse events related to hyperkalemia.
9. The CLASS trial data do not support the conclusion that serious hepatic adverse events are more frequent in those patients taking celecoxib than diclofenac or ibuprofen. In fact, hepatic enzyme elevations and withdrawals for these elevations were significantly and consistently reduced compared to diclofenac.
10. The incidence of rash (generally mild or moderate, none were serious) was statistically significantly higher for celecoxib than for either diclofenac or ibuprofen. The incidence of pruritis was also statistically significantly higher for celecoxib than ibuprofen, but not diclofenac. The incidence of clinically significant rash with celecoxib was estimated to be 0.13%. The percentage of patients withdrawing for either rash or pruritis was generally higher in the celecoxib group.
11. There were no deaths from gastrointestinal, hepatic, renal or dermatologic causes in any treatment group during the time period of the CLASS trial.
12. No new safety issues were apparent regarding respiratory, endocrine/metabolic, CNS/PNS or infectious disease safety.
13. Celecoxib was generally safe and well tolerated at the supratherapeutic doses employed in this CLASS trial.
14. Overall safety, as defined by the endpoints of deaths, serious adverse events and withdrawals due to adverse events did not appear to be meaningfully or consistently different among the three treatment groups.

