**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, Cardiorenal 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 $HCO_3$ 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 $HCO_3$ <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.

**Hepatic events**

In the original NDA, it was noted that celecoxib did not appear to significantly alter liver or biliary function as determined primarily by elevations of enzymes and other laboratory measurements (i.e. ALT, AST, bilirubin, alkaline phosphatase). Serious adverse events were rare. However, cases of liver failure have been reported in post-marketing data.

The data in the CLASS trial appear to confirm that long-term use of high doses of celecoxib is not associated with significant elevations of enzymes or serious hepatic adverse events. However, diclofenac was associated with significant elevations of liver enzymes requiring withdrawal of approximately half of these patients. Of interest, there were no deaths from hepatobiliary causes in any treatment group in the CLASS trial.

**Dermatologic events**

In the original NDA, it was noted that rashes and related cutaneous reactions were among the more frequently noted adverse events associated with celecoxib treatment. The rashes were generally mild in severity, and often associated with urticaria or pruritis. Rash was the single most common reason for withdrawal from study treatment. There was an increase in incidence of rash at higher celecoxib doses (the highest being the dose used in this trial) that suggested a dose-response relationship. Importantly, there were no serious cutaneous reactions associated with celecoxib treatment.

In the CLASS database, the results appear to be similar to those of the original NDA. 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. Of note, there were no cases of Stevens Johnson syndrome, toxic epidermal necrosis or erythema multiforme noted for any of the treatment groups in this trial.

**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 ± 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.



**Labeling Review:**
By agreement, the revised labeling will be incorporated later as an amendment to this review or as a separate document.

**Financial Disclosure**
In accordance with 21 CFR part 54, a signed form 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) was included with the sNDA.

the remainder of the investigators were noted not to have participated in financial arrangements or hold financial interests required to be disclosed under 21 CFR part 54. Review of the clinically significant UGI events associated with the clinical investigators (appendix 3.6.1; N49_035_102) who had arrangements with the sponsor did not identify obvious differences from the remainder of these clinical events submitted in this sNDA.



## Appendix (CSUGIEs)

A narrative summary was prepared for each CSUGIE and symptomatic ulcer. The data for these summaries were derived from the CRFs and any additional medical records resulting from the work-up. The narrative summaries for all CSUGIEs that occurred at any time during study participation are included below. These are sorted by case number (case numbers were assigned chronologically in order of the reporting of potential CSUGIEs).

### Case 1000

**Patient US0293-035-10579** was a 69-year-old female with a history of hypertension, right-sided mastectomy, hysterectomy, non-insulin-dependent diabetes mellitus, and OA. Concomitant medications included atenolol, enalapril, and trazadone. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID**.

the patient had a surgical oversew of the lesion and ultimately recovered. She received a total of 9 units of packed red blood cells during the hospitalization. This event was classified as: **duodenal ulcer; GI bleed (traditional, 1B; alternate, 1F).**

## Case 1022

**Patient US0268-102-10193** was a 73-year-old female with a history of sinusitis, hyperopia, myopia, migraines, hypertension, colon polyps, cholecystectomy, inflamed ovary, breast cancer with no recurrence, leg cramps, intermittent elevation of liver enzymes, allergy to penicillin, and OA. Concomitant medications included hydrochlorothiazide, potassium, and calcium carbonate. The patient was enrolled in protocol N49-98-02-102 and randomized to **diclofenac 75 mg BID.**

After 8 days of treatment the patient began experiencing melena, abdominal pain and distention, nausea, dyspnea, and syncope. On study day 10 the patient was found to have a hemoglobin of 12.8 g/dL compared with a baseline hemoglobin of 13.4 g/dL and a hematocrit of 37.5% compared with a baseline hematocrit of 40.0%. **Study medication was discontinued on day 10**. Baseline serology for *H. pylori* had been positive. On study day 15 an endoscopy was performed revealing two gastric ulcers in the antrum measuring 0.3 cm and 0.2 cm. Also seen were superficial gastric erosions and streaking erythema in the distal body and one duodenal bulb erosion. This event was classified as: **gastric ulcer; GI bleed (traditional, 1C; alternate, none).**

## Case 1025

**Patient US0425-035-11153** was an 85-year-old female with a history of sleep disorder due to chronic pain, mild Parkinson's disease, diastolic dysfunction, upper respiratory infection/sinusitis, restrictive/obstructive lung disease, bleeding secondary to constipation, colon cancer, rectal bleeding due to constipation, diverticulosis, gastroesophageal reflux disease, hiatal hernia, urinary tract infection, bladder dysfunction, hysterectomy, osteoporosis, low back pain, excision of basal cell carcinoma, hypothyroidism, hyperlipidemia, anemia, intermittent mild thrombocytopenia, allergy to metoclopramide hydrochloride, and OA. Concomitant medications included levothyroxine, atorvastatin, diltiazem, aspirin, Darvocet N-100, oxybutynin, alendronate, multivitamin, and Citrucel. The patient was enrolled in protocol N49-98-02-035 and randomized to **celecoxib 400 mg BID**.

On study day 67 the patient presented to the clinic with a one-day history of passing melenic stools and complaints of lightheadedness and abdominal pain that had begun on that day. Findings at this time included hemoccult-negative stool, significant orthostatic changes in both systolic and diastolic blood pressure, and a hemoglobin of 12.0 g/dL compared with a baseline of 15.0 g/dL and a hematocrit of 36% compared with a baseline of 45%. The patient was admitted to the hospital and subsequently transferred to the intensive care unit after she became more hypotensive and tachycardia. The patient was transfused 2 units of packed red blood cells and an endoscopy was performed on study day 68. Endoscopic findings included a deep gastric ulcer with a visible vessel in the antrum measuring 0.5 cm in its longest length, duodenitis with multiple areas of submucosal hemorrhaging, and a superficial duodenal bulb ulcer measuring 1.5 cm at its longest length. Due to mechanical failure, thermal coagulation of the visible vessel was unsuccessful. On study day 70 the patient's hemoglobin had fallen to 8.9 g/dL and the hematocrit had fallen to 26.9%. A repeat endoscopy was performed. This exam revealed similar findings to the previous endoscopy with the additional finding of a 1.0-cm clean-based postbulbar ulcer. Again, no active bleeding was present and the gastric ulcer with visible vessel was treated with several applications of Gold Probe coagulation. Biopsies obtained for *H. pylori* from the antrum were negative, as was the baseline serology. Over the next several days the patient stabilized and was discharged on study day 73; **study medication had been discontinued on day 62**. This event was classified as: **gastric ulcer; GI bleed and duodenal ulcer (traditional, 1B; alternate, 1F).**

## Case 1026

**Patient US0080-035-12446** was a 75-year-old female with a history of splenectomy, hysterectomy, onychomycosis of both feet, water retention, hypothyroidism, and OA. Concomitant medications included estradiol, levothyroxine, and spironolactone hydrochlorothiazide. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID.**

After 5 days of treatment the patient developed melenic stools. Black, tarry stools continued into study day 6 and on study 7 the patient was seen in the investigator's office. Significant findings at this time included hemoccult-positive

diameter, was found in the prepyloric area. None of the ulcers had stigmata of recent bleeding and no fresh blood was seen. Finally, the gastric mucosa appeared generally inflamed and the antrum was described as "abnormal." A CLOtest biopsy was negative for *H. pylori*, as was the baseline serology. The **patient was terminated from the study and treated with acid suppression**. A follow-up endoscopy done approximately six weeks later revealed a 0.5-cm antral ulcer approximately 3 to 4 cm from the pylorus. CLOtest was again negative. This event was classified as: **gastric ulcer; GI bleed (traditional, 1C; alternate, none).**

***Reviewer's comment: The dates/comments in this summary that appear in [] were added after review of the CRF.***

## Case 1036

**Patient US0017-102-10032** was an 80-year-old male with a history of impaired hearing, cataracts in right and left eyes, Parkinson's disease, anxiety, right carotid endarterectomy, hypertension, bilateral common carotid angiography, appendectomy, peptic ulcer in 1988, heartburn, rash under right breast, and OA. Concomitant medications included enalapril maleate, Darvocet-N, amantadine hydrochloride, isradipine, and clonazepam. The patient was enrolled in protocol N49-98-02-102 and randomized to **diclofenac 75 mg BID.**

After 66 days of treatment the patient began experiencing diarrhea and very dark black stool. Significant findings at this time included hemoccult-positive stool and a hemoglobin of 14.3 g/dL compared with a baseline of 14.5 g/dL and a hematocrit of 44% compared with a baseline of 43%. On study day 72, an upper endoscopy revealed fewer than 25 red- and white-based erosions scattered in the gastric body and antrum, but most prominently located in the prepyloric area. There was also a white-based linear ulceration measuring 0.3 cm in length on the posterior wall of the pylorus. The duodenal bulb and sweep were remarkable for patchy areas of inflammation. Also seen was a small sliding hiatal hernia. There was no evidence of esophagitis. Serology for *H. pylori* was negative, as was the baseline serology. **Study medication was discontinued on day 66.** This event was classified as: **gastric ulcer; GI bleed (traditional, 1C; alternate, none).**

## Case 1037

**Patient US0386-102-10294** was a 71-year-old female with a history of a right wrist ganglion, migraine headaches and intermittent headaches, dizziness, transient ischemic attack, hypertension, carotid artery stenosis, peripheral vascular disease, aortofemoral bypass, emphysema, dyspepsia, duodenal ulcer, gastric ulcer, esophagitis, chronic constipation, hemorrhoids, intermittent rectal bleeding, cystocele repair, hysterectomy, compound fracture of the 4th lumbar vertebra, back pain, left small toe fracture, hypercholesterolemia, osteoporosis, and OA. Concomitant medications included nifedipine slow release, lisinopril, dipyridamole, and hydrochlorothiazide. The patient was enrolled in protocol N49-98-02-102 and randomized to **diclofenac 75 mg BID.**

After nine days of treatment the patient began experiencing epigastric pain, nausea, and heartburn. At this time the patient was found to have hemoccult-positive stool. Endoscopic evaluation performed on study day 30 revealed a 1.0-cm duodenal bulb ulcer with a clot. **Study medication was discontinued** at this time. Serology for *H. pylori* was negative, as was the Baseline serology. This event was classified as: **duodenal ulcer; GI bleed (traditional, 1B; alternate, none).**

## Case 1040

**Patient US0024-102-20702** was a 73-year-old male with a history of hearing loss, tonsillectomy, chronic sinusitis, septal deviation, concha bullosa deformities of both middle turbinates, arcuate defects of both eyes, numbness and tingling in left leg, appendectomy, hemorrhoids, benign prostatic hyperplasia, muscle weakness, low back pain, fracture of the right ankle, shrapnel scars, bruising easily, lips burning, anemia, hepatitis, hyperuricemia, hypercholesterolemia, OA, and RA. Concomitant medications included hydrocodone bitartrate with acetaminophen, prednisone, methotrexate, hydrochlorothiazide with triamterene, diphenhydramine hydrochloride cream, aspirin, Tums, multivitamins, and Folic acid. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID.**

Biopsy was negative for *H. pylori,* as was a Baseline serology. The patient was treated with acid suppression and was **discontinued from the study.** This event was classified as: **duodenal ulcer; GI bleed (traditional, 1C; alternate, 1G).**

## Case 1056 (Censored)

**Patient US0114-035-11573** was a 72-year-old female with a history of myopia, hyperopia, sinus infection, glaucoma, tonsillitis, temporal mandibular joint dysfunction, stress headaches, depression, migraines, hypertension, hypercholesterolemia, pneumonia, bronchitis, hiatal hernia, urinary tract infection, menorrhagia, benign bilateral breast cysts, shattered humerus, dehydration and OA. Concomitant medications included Levo Bunolol, medroxyprogesterone acetate, conjugated estrogen, triamterene, verapamil hydrochloride, fluoxetine hydrochloride, Fioricet, Calcium with Vitamin D, Darvocet, Vitamin C, and loratadine. The patient was enrolled in protocol N49-98-02-035 and randomized to **celecoxib 400 mg BID**.

[The patient started therapy on 12/11/98. This may also be the last day of her prior naproxen sodium therapy]. After 2 [rash was noted first on study day 9-12/19/98 or study day 11-12/21/98] days of treatment the patient developed itching, a whole body rash, and black stools [melena was first noted by the patient 12-19-98 at which time she was found to be heme +, a typed addition to the CRF states that "it is believed patient began having black stools on 12/12.98"]. From study day 10 through study day 16 the patient complained of GI upset. **Study medication was discontinued on day 10 [day 11-12/21/98].** At this time the patient was given a prescription for cimetidine and a steroid dose pack. She refused further work-up until "after the holidays" and ultimately returned for a termination visit on day 27 [1/6/99]. Significant findings at this time included a hemoglobin of 10.2 g/dL compared with a baseline of 12.3 g/dL, a hematocrit of 29.0% compared with a baseline of 37.0%, and hemoccult-positive stool. A UGI endoscopy was performed on day 50 [1/29/99] revealing 0.5-cm and 0.3-cm clean-based antral ulcers, and an erosion on the greater curve in the mid-body of the stomach. A biopsy for *H. pylori* was negative, as was the baseline serology. Of note, the patient did not take any NSAIDs between study drug discontinuation and the endoscopy. This event was classified as: **gastric ulcer; GI bleed (traditional, 1C; alternate, 1G).**

> ***Reviewer's comment: The dates/ comments in this summary that appear in* [] *were added after review of the CRF.***

## Case 1057

**Patient US0268-102-10196** was a 60-year-old male with a history of tinnitus, decreased hearing in right ear, hypertension, mild restrictive lung disease, hiatal hernia, colon polyps, rotator cuff injury of the right shoulder, bilateral ankle and groin rash secondary to dermatitis, and OA. Concomitant medications included amlodipine besylate, levothyroxine sodium, diazepam, Tylenol PM, fluoxetine hydrochloride, Tylenol with Codeine, and nizatidine. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID.**

After 56 days of treatment the patient began experiencing severe epigastric pain. **Study medication was discontinued on day 62.** On study day 65 the patient underwent an UGI endoscopy revealing a large hiatal hernia and a 1.0 to 1.2-cm duodenal bulb ulcer with adherent clot in the base. Serology for *H. pylori* was negative, as was the baseline serology. The patient was **discontinued from the study** and treated with acid suppression.
This event was classified as: **duodenal ulcer; GI bleed (traditional, 1B; alternate, 1F).**

## Case 1058

**Patient US0118-102-20035** was a 56-year-old female with a history of hysterectomy, multiple fractures as a result of an automobile accident, *Staphylococcus* infection, and RA. Concomitant medications included hydroxychloroquine sulfate, conjugated estrogens, and sulfasalazine. The patient was enrolled in protocol N49-98-02-102 and randomized to **diclofenac 75 mg BID**.

After 6 days of treatment the patient began experiencing nausea and moderate to severe abdominal pain. **Study medication was discontinued on day 19.** On study day 20 the patient underwent an upper endoscopy revealing six antral ulcers, the largest measuring 0.6 x 0.2 cm with a small overlying clot. The remaining five ulcers measured 0.2 to 0.4 cm. A small hiatal hernia, ulcerative esophagitis, and duodenitis were also reported. A biopsy for *H. pylori* was positive, as was the baseline serology. The patient was **discontinued from the study** and treated with acid suppression. This event was classified as: **gastric ulcer; GI bleed (traditional, 1B; alternate, none).**

darvocet, calcium, and multiple vitamins. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID.**

After 107 days of treatment the patient began experiencing dyspnea on exertion, diaphoresis, hematochezia, and melena. **Study medication was discontinued** on day 108. On study day 113 the patient presented to the clinic and was admitted to the hospital. Significant findings at this time included a hematocrit of 25.3% compared with a baseline hematocrit of 38.0%. The patient received 2 units of packed red blood cells. Upper GI endoscopy performed the next day, study day 114, revealed a deep linear ulcer in the prepyloric antrum with surrounding edema. There was also a deep, round duodenal bulb ulcer 1.0 cm in diameter. Both ulcers had an exudative base without stigmata of recent bleeding. A CLOtest was negative for *H. pylori,* as was the baseline serology. The patient was treated with acid suppression. This event was classified as: **gastric ulcer, duodenal ulcer; GI bleed (traditional, 1C; alternate, 1G).**

## Case 1084

**Patient US0052-102-10549** was an 84-year-old female with a history of dry eyes secondary to Sjogren's syndrome, appendectomy, flatulence, irritable bowel syndrome, lysis of intestinal adhesions, incontinence, hysterectomy, chronic urinary tract infections, osteoporosis, left shoulder tendonitis, right hip replacement, bilateral hammertoe repair, hair loss, and OA. Concomitant medications included conjugated estrogens, multivitamins, calcium carbonate, loperamide, and aspirin. The patient was enrolled in Study N49-98-02-102 and randomized to **diclofenac 75 mg BID.**

After 93 days of treatment the patient was seen in the clinic for a scheduled week 13 visit and found to have a hemoglobin of 9.6 g/dL compared with a baseline of 11.9 g/dL and a hematocrit of 28.0% compared with a baseline of 37.0%. On study day 97 a stool sample was found to be hemoccult-positive. **Study medication was discontinued at this time.** On study day 98 a UGI endoscopy was performed revealing four very shallow erosions in the prepyloric antrum and a 1.0-cm shallow to moderately deep ulcer in the distal duodenal bulb. The ulcer had a clean base but a small amount of blood was noted to ooze from the periphery of the lesion. A biopsy for *H. pylori* was negative despite a positive baseline serology. The patient was treated with acid suppression and **discontinued from the study.** This event was classified as: **duodenal ulcer; GI bleed (traditional, 1B; alternate, 1F).**

## Case 1085

**Patient US0110-035-11139** was a 67-year-old male with a history of Meniere's disease, hyperlipidemia, chronic obstructive pulmonary disease, cerebrovascular accident, asthma, anserine bursitis of right knee, central laminectomy, type II diabetes mellitus, thoracic outlet syndrome, rib resection, right knee arthroscopy, right tennis elbow, seasonal and environmental allergies, allergy to penicillin, and OA. Concomitant medications included pravastatin, meclizine, metformin, Asthmacort, albuterol, aspirin, methylprednisolone, and loratadine. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID**.

After 168 days of treatment the patient called the principal investigator because he was feeling weak and dizzy. He also reported black stools and leg cramps. Because the patient felt too sick to see the investigator, he presented to the emergency room. The patient repeated his concerns about orthostatic symptoms and reported persistent melena. Significant findings at this time included pallor, tachycardia with a heart rate of approximately 130 to 140 bpm, and black, hemoccult-positive stool. A nasogastric lavage produced "coffee ground" material. A hemoglobin was 13.0 g/dL compared with a baseline 15.3 g/dL and a hematocrit was 40.1% compared with a baseline of 45.0%. The patient was admitted to the hospital and a UGI endoscopy performed that evening revealed old blood but no active bleeding, a linear distal esophageal ulcer, a group of shallow antral ulcers, and a pyloric channel ulcer with a visible vessel. The visible vessel was cauterized with a heater probe. No *H. pylori* testing was done, but the baseline serology had been positive for *H. pylori*. **Study medication was discontinued** and the patient was treated with acid suppression. This event was classified as: **gastric ulcer; GI bleed (traditional, 1B; alternate, 1F).**

## Case 1113

**Patient US0112-035-10235** was an 84-year-old female with a history of coronary artery bypass graft secondary to coronary artery disease, hypertension, benign heart murmur, hiatal hernia, colon resection secondary to infection, hysterectomy, osteoporosis, left knee replacement, psoriasis, and OA. Concomitant medications included alendronate

sodium, diltiazem hydrochloride, aspirin, furosemide, vitamin B12, vitamin D, fluvastatin sodium, isoxsuprine hydrochloride, calcium carbonate, and potassium chloride. The patient was enrolled in protocol N49-98-02-035 and randomized to **celecoxib 400 mg BID.**

After 209 days of treatment the patient developed nausea, anorexia, and right upper quadrant pain. On study day 210 the patient presented to her primary care physician and a work-up including an abdominal ultrasound and abdominal CT was performed. The ultrasound revealed a small amount of fluid in Morrison's pouch and the CT revealed a prominent gallbladder with pericholecystic fluid. An x-ray revealed free air in the right upper quadrant and an exploratory laparotomy revealed a perforated pyloric channel ulcer. A Graham closure was performed and the patient recovered without incident. The baseline serology had been negative for *H. pylori*. **Study medication was discontinued** on day 211. This event was classified as: **gastric ulcer; perforation (traditional, 2; alternate, 2).**

## Case 1122

**Patient US0448-035-11767** was a 68-year-old female with a history of bilateral cataract removal with lens implants, heartburn, back and neck pain, arthroscopic right knee surgery, psoriasis, sun sensitivity, and OA. Concomitant medications included conjugated estrogen, medroxyprogesterone acetate, carisoprodol, calcium, vitamins, Pain Free herbal supplement, acetaminophen, and l-lysine. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID.**

After 123 days of treatment the patient began experiencing abdominal pain. She reported that on study day 124 she vomited for 5 hours but obtained some relief from Mylanta. On study day 126 the patient presented to her physician and was found to be hemoccult-positive. **Study medication was discontinued** at this time. A hemoglobin at this time was 11.3 g/dL compared with a baseline of 12.3 g/dL and a hematocrit was 33.7% compared to a baseline of 37.0%. On study day 129 the patient underwent UGI endoscopy revealing four posterior wall antral ulcers, the largest of which was 0.8 cm x 1.0 cm, three proximal antral ulcers between 0.3 cm and 0.6 cm located along the lesser curvature, a 0.2 x 1.5-cm greater curvature erosion, multiple punctate erosions, a 0.6-cm to 0.7-cm pyloric channel ulcer, and a normal duodenum to the third portion. The endoscopist felt that there was no evidence of outlet obstruction but that the pyloric channel ulcer may have contributed to a partial outlet obstruction. Biopsy for *H. pylori* was negative, as was the baseline serology. This event was classified as: **gastric ulcer; GI bleed (traditional, 1D1; alternate, none).**

## Case 1132

**Patient US0371-035-12217** was a 78-year-old female with a history of cataract removal with lens implant, memory loss, internal hemorrhoids, colo-vesicular fistula, gastroesophageal reflux, appendectomy, coronary artery disease, angina pectoris, family history of colon carcinoma, sigmoid resection for chronic diverticulitis, hiatal hernia, urinary incontinence, degenerative joint disease, right inguinal hernia repair, fibrocystic breast disease, obesity, allergy to eggs, and OA. Concomitant medications included Centrum vitamins. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID.**

After 25 days of treatment the patient began experiencing epigastric pain and reflux. She was found to have a hemoglobin of 10.2 g/dL compared with a baseline of 12.3 g/dL and a hematocrit of 30.0% compared with a baseline of 36.0%. Stool hemoccults were negative and on study day 30 a UGI series revealed a large hiatal hernia with reflux. The patient remained in the study and on study day 81 she had a colonoscopy revealing hemorrhoids, an anastomotic stricture and diverticulosis. On a routine study visit on study day 92 the patient was found to have a persistently low hemoglobin of 9.7 g/dL with a hematocrit of 31.0% and on study day 99 the stool was hemoccult-positive for the first time. **Study medication was discontinued** on day 141 and on study day 149 a UGI endoscopy revealed a hiatal hernia and a 0.3 to 0.4-cm gastric ulcer in the proximal body with associated black spot or blood clot. Biopsy for *H. pylori* was positive, as was the baseline serology. The patient was treated with antibiotics and acid suppression. This event was classified as: **gastric ulcer; GI bleed (traditional, 1B; alternate, 1F).**

## Case 1133

**Patient US0182-102-11142** was a 66-year-old female with a history of angina, heart attack, hypertension, constipation, hemorrhoid, hysterectomy, osteoporosis, total right and left hip arthroplasty, redone total left hip arthroplasty, and OA. Concomitant medications included lisinopril, diltiazem hydrochloride, conjugated estrogens, vitamin supplement, Vitamin C, Vitamin E, and docusate sodium. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID.**

packed red blood cells on study days 278 and 280. On day 284 the patient had a witnessed black diarrheal stool that was found to be hemoccult-positive. Colonoscopy performed on study day 286 revealed multiple diverticuli in the sigmoid colon and a poor preparation in the right colon. No bleeding was identified on this examination. Baseline serology for *H. pylori* had been positive. This event was classified as: **gastric ulcer; perforation (traditional, 2; alternate, 2).**

## Case 1343

**Patient US0514-102-12391** was a 61-year-old female with a history of nasal fracture, tonsillectomy, depression, hypercholesterolemia, seasonal allergies, dyspnea, cholecystectomy, occasional heartburn, hiatal hernia, esophageal sphincter stenosis surgery, gastric ulcer oversew, surgical removal of gastric scar tissue, duodenal ulcer, bulimia, diverticulosis (inactive), appendectomy, hysterectomy, fibrocystic breast disease, fractured pelvis, back pain, thin dry skin on arms, lipoma removal, chronic anemia, and OA. Concomitant medications included vitamin B12, trazodone hydrochloride, bupropion, diazepam, conjugated estrogens, Tylenol Sinus, St. Johns Wort, Tums, and Darvocet N-100. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID.**

After 261 days of treatment, at a routine visit, she was found by the Investigator to have epigastric tenderness and a hemoglobin of 9.8 g/dL compared with a baseline of 12.7 g/dL and a hematocrit of 32.0%, compared with a baseline of 41.0%. **Study medication was discontinued at this time**. In addition, on study day 249, stool was reported as hemoccult-positive. Baseline serology for *H. pylori* had been negative. On study day 262 an endoscopy revealed grade II nonerosive esophagitis and evidence of a partial gastrectomy. There was food residue in the stomach and a high-grade strictured region with erosive, friable, and white mucosa at the body of the stomach. The anastomotic area mucosa was friable, but no obvious old or new bleeding was seen. The endoscope could not be passed through the stenotic anastamosis. On study day 268, the patient underwent repeat endoscopy for vomiting, weight loss, and nausea. During balloon dilatation of the anastamosis a perforation occurred in the stomach requiring discontinuation of the procedure and hospitalization. The patient was transferred to the hospital for management of the perforation. Computerized tomography confirmed a perforated viscus with free peritoneal air. The patient underwent an emergency laparotomy, lysis of adhesions, and stricturoplasty with repair of perforation and patch. The patient received 2 units of blood perioperatively. Postoperative recovery was uneventful. This event was
classified as: **gastric outlet obstruction (traditional, 3; alternate, 3).**

## Case 1356

**Patient US0321-102-10761** was a 72-year-old female with a history of cardiovascular disease, recurrent sore throat, laryngitis, hypertension, hypercholesterolemia, II/IV systolic ejection murmur, bilateral leg varicosities, pneumonia, external hemorrhoids, menopause, left hip and leg pain, angioma of the right buttock, lumbar spondylosis, and OA. Concomitant medications included atenolol, hydrochlorothiazide, and acetaminophen. The patient was enrolled in protocol N49-98-02-102 and randomized to **celecoxib 400 mg BID.**

After 307 days of treatment the patient began experiencing nausea, vomiting, and diarrhea. On study day 316, the patient was admitted to the hospital with complaints of nausea, coffee ground emesis, burning in her throat, a bad taste in her mouth, diarrhea, and fever. **Study medication was discontinued**, and significant findings at this time included a hemoglobin of 9.7 g/dL compared with a baseline of 12.1 g/dL and a hematocrit of 28.0%, compared with a baseline of 36.0%, and hemoccult-positive stool. On study day 317, the patient developed right upper quadrant abdominal and epigastric discomfort and a temperature elevation to 103.7°F. On day 318, the patient underwent abdominal ultrasound with normal results. On day 319, the patient underwent an endoscopy that revealed a hiatal hernia, grade I esophagitis, atrophic gastropathy, multiple dispersed erosions with stigmata of recent bleeding, evidence of dark blood in the incisura, antrum, and prepyloric region, two nonbleeding linear antral ulcers, and a normal duodenum. The largest dimension of the gastric ulcers was 0.7 cm. Baseline serology for *H. pylori* had been negative. The patient was treated with acid suppression and **discontinued from the study** with a work-up planned to determine the etiology of the fever. This event was classified as: **gastric ulcer; GI bleed (traditional, 1A; alternate, 1E).**

## Case 1383 (Censored)

**Patient CA0484-035-12170** was a 62-year-old male with a history of hypertension, ischemic heart disease, tachyarrythmias, cholecystectomy, peptic ulcer disease, elevated liver enzymes, diffuse idiopathic skeletal hyperostosis, gout, rotator cuff surgery, headaches, renal dysfunction, and OA. Concomitant medications included allopurinol,

atenolol, Cytotec, vitamin E, calcium, and magnesium. The patient was enrolled in protocol N49-98-02-035 and randomized to **ibuprofen 800 mg TID.**

After 18 days of treatment the patient began experiencing diffuse abdominal pain, bloating, acid regurgitation, and severe retrosternal burning. **Study medication was discontinued at this time**. After study medication was discontinued on day 18, the patient took **indomethacin SR 75 mg from study day 22 to day 34** . On day 21 stool was hemoccult-negative. On study day 29 a hemoglobin was unchanged from baseline at 14.5 g/dL and a hematocrit was 44.0% compared with a baseline of 42.2%. On study day 36 the patient developed black tarry stools and weakness. On study day 43 an endoscopy was performed revealing a slight laxity at the diaphragmatic pinch, and a linear, 1.0-cm duodenal bulb ulcer. According to the endoscopist, the ulcer appeared to be healing. A biopsy for *H. pylori* was negative, despite a positive baseline serology. A hemoglobin and hematocrit on the day of endoscopy was 12.4 g/dL and 36.0%, respectively. Additionally, stools were hemoccult positive on study days 41 and 42. The patient was treated with acid suppression and for *H. pylori* and **discontinued from the study**. This event was classified as: **duodenal ulcer; GI bleed (traditional, 1C; alternate, 1G).**

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Jonca Bull
6/20/01 08:04:17 PM
MEDICAL OFFICER

# CARDIO-RENAL REVIEW

## 0.0 RÉSUMÉ


**Effect of Celecoxib on Acid-Base Balance**

In the original NDA database, the effect of celecoxib on serum bicarbonate ($HCO_3$) was not assessed. There was some evidence of an association between celecoxib use and an increase in serum chloride, which can be interpreted as related to fall in serum $HCO_3$. To address this issue, the sponsor measured changes in serum $HCO_3$ in CLASS and collected adverse events related to changes in systemic acid-base balance. In the analysis (detailed below) between 1 and 2% of the subjects in all three treatment groups had a measured serum $HCO_3$ <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 agents. In addition, there was no increase in reported clinical adverse events related to changes in acid-base balance in the celecoxib group: such adverse events were quite rare in the database for all three drugs. Overall, then, celecoxib, diclofenac and ibuprofen use have been associated with changes in renal acid-base handling, perhaps related to inhibition of COX-1 and COX-2 in the kidney. The CLASS database contains no evidence for an adverse effect of celecoxib on acid-base balance relative to either diclofenac or ibuprofen.

**Comparative Incidence of Renal Adverse Effects for Celecoxib, Diclofenac and Ibuprofen**

The rates of reported clinical renal adverse events were low in the database, and there was no consistent clinically-significant 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. In the CLASS database the renal adverse event profile for celecoxib was not clearly different from that of NSAIDs (as represented by diclofenac and ibuprofen). This includes adverse events reported by investigators (*e.g.*, worsened hypertension or edema, uremia) and those detected through routine laboratory or bl ood pressure measurements (*e.g.*, increased BUN/ Crt or systolic blood pressure).

**Comparative Incidence of Cardiac Adverse Effects for Celecoxib, Diclofenac and Ibuprofen**

While there were some differences in the rates of reported clinical cardiac adverse events between the three treatment groups, there was no consistent clinically-significant adverse effect of celecoxib in the reported parameters of cardiac safety when compared with either diclofenac or ibuprofen. Particular concern has been raised regarding a possible pro-thrombotic effect of selective inhibition of COX-2 (for example, by celecoxib). In CLASS, the incidence of adverse events related to cardiac ischemia was higher in the celecoxib group when compared with the two comparators. This difference was most pronounced in the group of patients not taking ASA. However, the differences observed in the rates of adverse events were small and relied on relatively few events. Importantly, the rate for serious adverse events related to cardiac ischemia and for cardiovascular mortality were not increased in the celecoxib group, although the rate of a combined group of adverse events reflecting anginal episodes was highest in the celecoxib group. In the patient population studied in CLASS, these findings exclude a large adverse effect of celecoxib on cardiovascular mortality compared with two non-selective COX inhibitors/ NSAIDs. These findings do not exclude a less significant effect of celecoxib on blood flow leading to less serious clinical outcomes and manifest by differences in the rates for less serious adverse events. In the CLASS database the overall cardiac adverse event profile for celecoxib was not clearly different from that of NSAIDs (as represented by diclofenac and ibuprofen).

**Effect of Aspirin Use on Adverse Events in CLASS**

Comparing the effects of the three drugs used in CLASS was complicated by the use of aspirin (ASA) in a sub-group of patients. As the trial randomization was not stratified for ASA use and the amount of ASA used by the patients who took it is not known, comparisons of the ASA- and non-ASA-users have limited power, and can detect only large differences between these two groups. In general, celecoxib, diclofenac and ibuprofen had similar rates of adverse events, regardless of whether the patient also used ASA. Patients who used ASA in all three treatment groups had a higher incidence of worsened hypertension, hyperkalemia and increases in BUN than patients who did not use ASA.

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## 1.0 Background and Methods

This consultation is focused on the renal and cardiac effects of celecoxib, based on data from a recently completed outcome trial in patients with rheumatoid- and osteo-arthritis: the Celecoxib Long-term Arthritis Safety Study (CLASS). Interest in the effects of celecoxib in on the kidneys and the cardiovascular system comes first from concerns about the comparative safety of selective inhibitors of cyclo-oxygenase type 2 (COX-2) such as celecoxib and rofecoxib, and non-selective COX inhibitors ( *e.g.*, ibuprofen, diclofenac). In addition concerns have been raised about a possible pro-thrombotic effect of the selective COX-2 inhibitors. This is based, in part, on the data in the original NDA databases (see below) and from investigations published since celecoxib's approval (references appear at the end of this review). These investigators have raised a concern about the effect of unopposed inhibition of COX-2 enzyme, leading to decreased production of prostacyclin (a vasodilator), without the combined inhibition of COX-1 (which would prevent platelets from being activated). Two large active-control trials have been performed that are relevant to this issue: CLASS (celecoxib) and VIGOR (rofecoxib). This consultation is restricted to an analysis of CLASS.

Cardiac Effects of Celecoxib

In my original consult on celecoxib performed as part of the initial NDA submission, I examined the cardiac laboratory data and adverse events and reached the following conclusions:

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

With regard to **cardiovascular adverse events**, there is an association between celecoxib administration and **worsened hypertension** in susceptible individuals. This effect of celecoxib resembles that of other non-steroidal anti-inflammatory drugs (NSAIDs). There was also an association between celecoxib administration and the development of clinically significant **edema**, again similar to other NSAIDs" (12.10.98).

Renal Effects of Celecoxib

In my original consult on celecoxib performed as part of the initial NDA submission, I examined the renal laboratory data and adverse events and reached the following conclusions:

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

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

**1.0 BACKGROUND AND METHODS (cont)**

Renal Effects of Celecoxib (cont)

While there were no clear cases of celecoxib-induced renal failure requiring dialysis in the controlled database, there were several individuals taking celecoxib who were withdrawn from the long-term open-label trial because of renal adverse events, including acute renal failure (as well as edema and worsening hypertension). It remains to be determined whether severe renal injury will occur following celecoxib at the same rate that is seen with other NSAIDs.

While a through comparison of the renal effects of celecoxib and other NSAIDs has not been performed, the available data suggest that celecoxib resembles other NSAIDs in the majority of the renal effects examined in the NDA. Further, the available data suggest that the renal effects of celecoxib are clearly distinguished from placebo" (12.10.98).

CLASS

CLASS compared the effects of high doses of celecoxib (400 mg BID) with those of ibuprofen (800 TID) and diclofenac (75 mg BID) in patients with osteoarthritis and rheumatoid. Patients could be treated with aspirin (ASA) if indicated for other medical conditions. Any patient who received ASA during the first 6 months of the study was counted as taking ASA, as opposed to counting only those patients taking ASA on a chronic basis. For details of the trial design the reader is referred to the Medical Review of the trial by James Witter, M.D., Ph.D. The current review will focus on the renal and cardiac safety data, and compare the incidence of laboratory changes and adverse events for celecoxib, ibuprofen and diclofenac.

The data for the cardiac and renal adverse events will be broken into a section on clinical adverse events, detected through spontaneous reporting and a section on changes detected in laboratory measurements, performed routinely throughout the trial period. Given the potential relevant interaction of celecoxib with ASA, special attention will be paid to an analysis based on the concomitant use of ASA.

**2.0 to 2.2 REVIEW OF CLINICAL DATABASE FROM CLASS**

**2.0 DEMOGRAPHICS AND METHODS**

For details regarding the CLASS protocol and methods the reader is referred to the review by James Witter, M.D., Ph.D.

**2.0a Extent of Exposure and Demographics**

Total exposure to the three treatments in the study is summarized in the table below.

**Table 2.0a.1 Exposure to Study Drugs in CLASS [a].**

| Treatment Group | Patients Exposed | Patient-Years of Exposure |
|---|---|---|
| **Celecoxib 400 mg BID** | 3987 | 2340 |
| **Diclofenac 75 mg BID** | 1996 | 1080 |
| **Ibuprofen 800 mg TID** | 1985 | 1122 |

a. Data from CLASS electronic submission, NDA 20-998.

This exposure included around a third of the patients in each group who received study drug for ≤3 months, as well as about half of each patient group who received the study drug for between 9 and 15 months. The study contains around 2300 patients treated with celecoxib, 1100 treated with diclofenac, and 1000 treated with ibuprofen for ≥6 months.

**Table 2.0a.2 Exposure to Study Drugs by Interval [a].**

| Interval on Drug | Celecoxib | Diclofenac | Ibuprofen |
|---|---|---|---|
| **≤3 months** | 1202 (30%) | 621 (31%) | 715 (36%) |
| **3-6 months** | 467 (12%) | 262 (13%) | 246 (12%) |
| **6-9 months** | 291 (7%) | 136 (7%) | 130 (7%) |
| **9-12 months** | 1442 (36%) | 913 (46%) | 415 (21%) |
| **12-15 months** | 585 (15%) | 64 (3%) | 477 (24%) |
| **>15 months** | 0 (0%) | 0 (0%) | 2 (<1%) |

a. Data from CLASS electronic submission, NDA 20-998 table 10.a.

**2.0b Collection of Adverse Events and Laboratory Measures in the Trial**

**Collection of Clinical Adverse Events**

Clinical adverse events were collected and reported by the investigators to the sponsor throughout the period of the trial. Adverse events were not centrally-adjudicated.

**Collection of Adverse Events Related to Laboratory Measurements**

Labs were to be collected at baseline and again at weeks 4, 13, 26, 39, 52, 65 and week 78 ('Final'). The number of patients with collected lab values varied between visits, as summarized below for selected renal parameters. Urinalyses were not collected routinely during the trial.

**2.0b Collection of Adverse Events and Laboratory Measures in the Trial (cont)**

**Table 2.0b.1 Number of Lab Measurements During CLASS [a].**

| | Celecoxib | | | Diclofenac | | | Ibuprofen | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | ASA | No ASA | Total | ASA | No ASA | Total | ASA | No ASA |
| **Week 4** | | | | | | | | | |
| **BUN/ Crt** | 3676 | 828 | 2986 | 1844 | 422 | 1438 | 1779 | 385 | 1423 |
| **Potassium** | 3629 | 820 | 2857 | 1820 | 418 | 1418 | 1757 | 380 | 1406 |
| **Bicarbonate** | 3670 | 827 | 2891 | 1838 | 421 | 1433 | 1774 | 384 | 1419 |
| **Week 26** | | | | | | | | | |
| **BUN/ Crt** | 2369 | 528 | 1889 | 1159 | 256 | 919 | 1059 | 236 | 852 |
| **Potassium** | 2347 | 523 | 1872 | 1149 | 256 | 909 | 1049 | 233 | 845 |
| **Bicarbonate** | 2366 | 527 | 1887 | 1153 | 255 | 914 | 1058 | 236 | 851 |
| **Final** | | | | | | | | | |
| **BUN/ Crt** | 3692 | 829 | 2911 | 1850 | 422 | 1444 | 1786 | 386 | 1429 |
| **Potassium** | 3673 | 824 | 2897 | 1837 | 420 | 1433 | 1770 | 383 | 1416 |
| **Bicarbonate** | 3689 | 829 | 2908 | 1845 | 421 | 1440 | 1782 | 385 | 1426 |

a. Data from CLASS electronic submission, tables 2.10.2.1, 2.10.4.1, and T44.1.

**2.1 RENAL AND CARDIAC SAFETY DATA FROM CLASS**

This section will examine four layers of potential adverse effects, beginning with the most serious (Total and Cardiovascular Mortality) and proceeding to Serious Adverse Events (SAEs), Adverse Events (AEs) including laboratory changes and blood pressure measurements, and then to Adverse Events leading to discontinuation.

**2.1a Total Mortality and Cardiovascular Mortality**

In the original NDA too few deaths occurred during the placebo-controlled period of the trials to be interpretable. In the long-term, open-label trial, cardiovascular mortality in deaths per patient-year was examined, arranged by highest dose of celecoxib used. The small numbers of patients obviously make interpretation of such calculated rates difficult, but there is an association between dose of celecoxib and the crude mortality rate due to cardiovascular causes.

**Table 2.1a.1 Cardiovascular Mortality Rates According to Highest Dose of Celecoxib Used, from the Long-term Trial [a].**

| Celecoxib Dose | Number of Deaths | Patient-years of Exposure | Crude Mortality Rate [b] |
|---|---|---|---|
| **100 mg** | 0 | 519 | [illegible] |
| **200 mg** | 4 | 1271 | [illegible] |
| **300 mg** | 2 | 340 | [illegible] |
| **400 mg** | 3 | 465 | [illegible] |

a. Data from original NDA Integrated Safety Summary, including Text Tables 65-68 and appendix 4.3.
b. Mortality (for both total and cardiovascular deaths) in deaths/pt-yrs (x100).

In similar fashion, the deaths in CLASS are summarized below, expressed in terms of deaths per person years of exposure to study drug. The majority of the results are based on materials submitted by the sponsor. The reader is referred to the Primary Medical Review by James Witter, M.D., Ph.D. for additional analyses based on individual case report review. Based on relatively few deaths, no excess mortality (total or cardiac) associated with celecoxib use is evident in any analysis.

**2.1a Total Mortality and Cardiovascular Mortality (cont)**

**Table 2.1a.2 Mortality Rates Per Person Years of Exposure From CLASS [a].**

| | Celecoxib N=3987/ 2320[d] | Diclofenac N=1996/ 1080[d] | Ibuprofen N=1985/ 1122[d] |
|---|---|---|---|
| **Deaths (All-Cause)** | 19 (0.8%) | 9 (0.8%) | 8 (0.7%) |
| **Deaths (All-Cause) on Study Drug[c]** | 8 (0.3%) | 5 (0.5%) | 3 (0.3%) |
| **Cardiac Deaths[b]** | 11 (0.5%) | 5 (0.5%) | 5 (0.4%) |
| **Cardiac Deaths on Study Drug[c]** | 5 (0.2%) | 4 (0.4%) | 3 (0.3%) |
| **Cardiac Deaths on Study Drug[e]** | 10 (0.4%) | 5 (0.5%) | 3 (0.3%) |

a. Data from electronic data submission, appendix 2.9.1 and pages 2918-3920 of vol. 24.
b. Deaths ascribed to ischemic cardiac causes (excluding 2 cases of CHF).
c. Excludes patients off of study drug for >28 days per the sponsor.
d. Number of patients enrolled/ patient-years of exposure.
e. Excludes patients off of study drug for >28 days per the Primary Medical Reviewer (James Witter, M.D., Ph.D.).

Given the concerns about the potential interaction of celecoxib and ASA (which inhibits COX-1), it is relevant to look at the mortality rates according to the use of ASA. Again, there is no signal for an increased mortality rate in the celecoxib group when compared with the two NSAIDs.

**Table 2.1a.3 Mortality Rates Per Person Years of Exposure From CLASS Stratified by ASA Use [a].**

| | Celecoxib N=3987/ 2320[c] | Diclofenac N=1996/ 1080[c] | Ibuprofen N=1985/ 1122[c] |
|---|---|---|---|
| **Deaths (All-Cause)** | | | |
| **ASA Users** | 6 (1.2%) | 1 (0.4%) | 4 (1.6%) |
| **Non-ASA Users** | 13 (0.7%) | 8 (1.0%) | 4 (0.5%) |
| **Cardiac Deaths on Study Drug[d]** | | | |
| **ASA Users** | 2 (0.4%) | 0 (0%) | 2 (0.8%) |
| **Non-ASA Users** | 3 (0.2%) | 4 (0.5%) | 1 (0.1%) |
| **Cardiac Deaths on Study Drug[e]** | | | |
| **ASA Users** | 5 (1.0%) | 0 (0%) | 2 (0.8%) |
| **Non-ASA Users** | 5 (0.3%) | 5 (0.6%) | 1 (0.1%) |

a. Data from electronic data submission, appendix 2.9.1 and pages 2918-3920 of vol. 24 and sponsor submissions to reviewer. Data relates to all reported deaths, irrespective of temporal relationship to last use of drug.
b. Deaths ascribed to ischemic cardiac causes per the sponsor (excluding 2 cases of CHF).
c. Number of patients enrolled/ patient-years of exposure.
d. Excludes patients off of study drug for >28 days per the sponsor.
e. Excludes patients off of study drug for >28 days per the James Witter, M.D., Ph.D.

**2.1b Serious Renal and Cardiac Adverse Events**

The next table summarizes the occurrence of selected serious adverse events (SAEs) relevant to renal and cardiac safety. There were no reported SAEs for acidosis or reduced serum bicarbonate reported. There were also very few reported renal SAEs. Cardiac SAEs were also uncommon, but the rate of reported serious "Combined Atrial SAEs" was higher in the celecoxib group than in the comparator groups. There was a higher rate of Myocardial infarctions (but not Anginal Disorders) in the celecoxib and ibuprofen groups when compared with diclofenac.

**Table 2.1b.1 Renal Serious Adverse Events (SAEs) per 100 Pt-Yrs Reported During CLASS [a].**

| Adverse Event | Celecoxib 400 mg BID n=3987 2320 Pt-Yrs | Diclofenac 75 mg BID N=1996 1080 Pt-Yrs | Ibuprofen 800 mg TID N=1985 1122 Pt-Yrs |
|---|---|---|---|
| **Hyper-, Hypo-kalemia[b]** | 0 (0%) | 0 (0%) | 0 (0%) |
| **Acidosis[b]** | 0 (0%) | 0 (0%) | 0 (0%) |
| **Nephrotic Syndrome[b]** | 0 (0%) | 0 (0%) | 0 (0%) |
| **Edema[b]** | 0 (0%) | 0 (0%) | 0 (0%) |
| **Uremia** | 0 (0%) | 0 (0%) | 1 (<0.1%) |
| **Renal Calculus** | 4 (0.2%) | 0 (0%) | 2 (0.2%) |

a. Data from electronic data submission, table T43.
b. These SAEs were not reported by investigators.

## 2.1b Serious Renal and Cardiac Adverse Events (cont)

**Table 2.1b.1 Cardiac Serious Adverse Events (SAEs) per 100 Pt-Yrs Reported During CLASS [a].**

| Cardiac SAEs | Celecoxib 400 mg BID n=3987 2320 Pt-Yrs | Diclofenac 75 mg BID N=1996 1080 Pt-Yrs | Ibuprofen 800 mg TID N=1985 1122 Pt-Yrs |
|---|---|---|---|
| **Atrial Arrhythmias** | | | |
| **Arrhythmia Atrial** | 2 (<0.1%) | 0 (0%) | 1 (<0.1%) |
| **Bradycardia** | 2 (<0.1%) | 0 (0%) | 0 (0%) |
| **Fibrillation Atrial** | 9 (0.4%) | 2 (0.2%) | 3 (0.3%) |
| **Tachycardia Supraventricular** | 3 (0.1%) | 0 (0%) | 0 (0%) |
| **Combined Atrial SAEs[b]** | 14 (0.6%) | 2 (0.2%) | 4 (0.4%) |
| **Angina** | | | |
| **Unstable Angina** | 8 (0.3%) | 4 (0.4%) | 0 (0%) |
| **Angina Pectoris** | 4 (0.2%) | 5 (0.5%) | 6 (0.5%) |
| **Coronary Artery Disorder** | 19 (0.8%) | 5 (0.5%) | 5 (0.4%) |
| **Combined Anginal Disorders[c]** | 30 (1.3%) | 14 (1.3%) | 10 (0.9%) |
| **Myocardial Infarction** | 19 (0.8%) | 4 (0.4%) | 9 (0.8%) |
| **Hypertension Aggravated** | 2 (<0.1%) | 0 (0%) | 0 (0%) |
| **Thrombophlebitis Combined[d]** | 8 (0.34%) | 6 (0.56%) | 1 (0.09%) |

a. Data from electronic data submission, table T43 and from sponsor at the request of the reviewer.
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.

For the renal SAEs, too few were reported to analyze according to the use of ASA. The table below summarizes the incidence of relevant cardiac SAEs according to the use of ASA.

**Table 2.1b.2 Serious Adverse Events (SAEs) per 100 Pt-Yrs Reported During CLASS [a].**

| Serious Adverse Event | Celecoxib | Diclofenac | Ibuprofen |
|---|---|---|---|
| **ASA Users** | N=882 517 Pt-Yrs | N=445 N=239 Pt-Yrs | N=412 249 Pt-Yrs |
| **Atrial Arrhythmias** | | | |
| **Arrhythmia Atrial** | 2 (0.4%) | 0 (0%) | 1 (0.4%) |
| **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 SAEs[c]** | 20 (3.9%) | 11 (4.6%) | 8 (3.2%) |
| **Myocardial Infarction** | 13 (2.5%) | 2 (0.8%) | 7 (2.8%) |
| **Non-ASA Users** | N=3105 1804 Pt-Yrs | N=1551 841 Pt-Yrs | 1573 874 Pt-Yrs |
| **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 SAEs[c]** | 10 (0.6%) | 3 (0.4%) | 2 (0.2%) |
| **Myocardial Infarction** | 6 (0.3%) | 2 (0.2%) | 2 (0.2%) |

a. 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.

**2.1c Renal and Cardiac Adverse Events**

**Clinical Renal Adverse Events**

The first table below summarizes the incidence of renal adverse events of interest reported by the investigators. These adverse events were reported in less than 2% of the patients, and occurred more or less equally in the three treatment groups. Related to the question of an effect of celecoxib on acid-base balance, no acidosis or low serum bicarbonate as clinical adverse events were reported. Similarly, in conditions of chronic acidosis, bony demineralization and fractures can occur. In CLASS, the rates of bony fractures were similar in the three treatment groups.

**Table 2.1c.1 Renal Adverse Events Reported During Study 35102 (CLASS) [a].**

| Adverse Event | Celecoxib 400 mg BID N=3987 | Diclofenac 75 mg BID N=1996 | Ibuprofen 800 mg TID N=1985 |
|---|---|---|---|
| **Lab Abnormalities** | | | |
| **BUN increased** | 45 (1.1%) | 34 (1.7%) | 18 (0.9%) |
| **Hypokalemia** | 15 (0.4%) | 10 (0.5%) | 23 (1.2%) |
| **Hyperkalemia** | 16 (0.4%) | 4 (0.2%) | 1 (<0.1%) |
| **Hyponatremia** | 12 (0.3%) | 4 (0.2%) | 4 (0.2%) |
| **Hypochloremia** | 6 (0.2%) | 1 (<0.1%) | 0 (0%) |
| **Hyperchloremia** | 1 (<0.1%) | 0 (0%) | 0 (0%) |
| **Hypophoshatemia** | 0 (0%) | 1 (<0.1%) | 2 (0.1%) |
| **Acidosis** | 0 (0%) | 0 (0%) | 0 (0%)[b] |
| **Alkalosis** | 2 (<0.1%) | 1 (<0.1%) | 2 (0.1%) |
| **Albuminuria** | 4 (0.1%) | 0 (0%) | 3 (0.2%) |
| **Hematuria** | 12 (0.3%) | 5 (0.3%) | 6 (0.3%) |
| **Clinical Adverse Events** | | | |
| **Pathologic Fracture** | 5 (0.1%) | 2 (<0.1%) | 7 (0.4%) |
| **Accidental Fracture** | 52 (1.3%) | 17 (0.9%) | 32 (1.6%) |
| **Renal Calculus** | 21 (0.5%) | 3 (0.2%) | 6 (0.3%) |
| **Uremia** | 1 (<0.1%) | 0 (0%) | 1 (<0.1%) |
| **Renal Failure, Acute** | 0 (0%) | 1 (<0.1%) | 0 (0%) |

a. Data from electronic submission, NDA 20-998 supplement S-009, Table T41.1.
b. Not reported by investigators for any patient.

**2.1c Reported Renal and Cardiac Adverse Events (cont)**

The next table summarizes selected adverse events according to the use of ASA. The rate of abnormal BUN was higher in all three treatment groups among patients who received ASA in combination with the NSAID/COX-2 Inhibitor. Other adverse events where the reported rate was >0.1% and >2X higher in the celecoxib group are shaded in the table below. Hyperkalemia as an AE was highest in the celecoxib group, regardless of the use of ASA.

**Table 2.1c.2 Selected Renal Adverse Events Reported During CLASS According to ASA Use [a].**

| Adverse Event | Celecoxib 400 mg BID | Diclofenac 75 mg BID | Ibuprofen 800 mg TID |
|---|---|---|---|
| *ASA-Users* | N=882 | N=445 | N=412 |
| **Lab Abnormalities** | | | |
| BUN increased | 19 (2.2%) | 14 (3.1%) | 5 (1.2%) |
| Hypokalemia | 2 (0.2%) | 2 (0.4%) | 3 (0.7%) |
| Hyperkalemia | 3 (0.3%) | 1 (0.2%) | 0 (0%) |
| Hyponatremia | 3 (0.3%) | 2 (0.4%) | 1 (0.2%) |
| Hypochloremia | 0 (0%) | 0 (0%) | 0 (0%) |
| Hyperchloremia | 0 (0%) | 0 (0%) | 0 (0%) |
| Hypophoshatemia | 0 (0%) | 0 (0%) | 1 (0.2%) |
| Albuminuria | 1 (0.1%) | 0 (0%) | 0 (0%) |
| Hematuria | 4 (0.5%) | 2 (0.4%) | 2 (0.5%) |
| **Clinical Adverse Events** | | | |
| Pathologic fracture | 0 (0%) | 1 (0.2%) | 2 (0.5%) |
| Accidental Fracture | 15 (1.7%) | 4 (0.9%) | 7 (1.7%) |
| Renal Calculus | 3 (0.3%) | 0 (0%) | 2 (0.5%) |
| Renal Failure, Acute | 0 (0%) | 0 (0%) | 0 (0%) |
| Uremia | 0 (0%) | 0 (0%) | 1 (0.2%) |
| *Non-ASA Users* | N=3105 | N=1551 | N=1573 |
| **Laboratory Abnormalities** | | | |
| BUN increased | 26 (0.8%) | 20 (1.3%) | 13 (0.8%) |
| Hypokalemia | 13 (0.4%) | 8 (0.5%) | 20 (1.3%) |
| Hyperkalemia | 11 (0.4%) | 3 (0.2%) | 1 (<0.1%) |
| Hyponatremia | 9 (0.3%) | 2 (0.1%) | 3 (0.2%) |
| Hypochloremia | 6 (0.2%) | 1 (<0.1%) | 0 (0%) |
| Hyperchloremia | 1 (<0.1%) | 0 (0%) | 0 (0%) |
| Hypophoshatemia | 1 (<0.1%) | 0 (0%) | 0 (0%) |
| Albuminuria | 3 (<0.1%) | 0 (0%) | 0 (0%) |
| Hematuria | 8 (0.3%) | 3 (0.2%) | 4 (0.3%) |
| **Clinical Adverse Events** | | | |
| Pathologic fracture | 5 (0.2%) | 0 (0%) | 5 (0.3%) |
| Accidental Fracture | 37 (1.2%) | 13 (0.8%) | 25 (1.6%) |
| Renal Calculus | 18 (0.6%) | 3 (0.2%) | 4 (0.3%) |
| Renal Failure, Acute | 2 (<0.1%) | 0 (0%) | 1 (<0.1%) |
| Uremia | 1 (<0.1%) | 0 (0%) | 0 (0%) |

a. Data from electronic submission, NDA 20-998 supplement S-009, Table T41.2 and T41.3.

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**2.1c Reported Renal and Cardiac Adverse Events (cont)**

The next table summarizes the reported rates of cardiac events of interest. None of the adverse events occurred at rates clearly higher in the celecoxib group when compared with the other two active treatments, although the rate of combined "Combined Anginal AEs" was highest in the celecoxib group. Edema was more commonly reported as an AE in the ibuprofen group, while the rates for celecoxib and diclofenac were similar.

**Table 2.1c.3 Cardiac Adverse Events Reported During CLASS [a].**

| Adverse Events (AEs) | Celecoxib 400 mg BID n=3987 | Diclofenac 75 mg BID n=1996 | Ibuprofen 800 mg TID n=1985 |
|---|---|---|---|
| **Edema** | | | |
| **Edema peripheral** | 146 (3.7%) | 70 (3.5%) | 104 (5.2%) |
| **Edema (pooled reporting)[b]** | 165 (4.1%) | 82 (4.1%) | 124 (6.2%) |
| **Cardiac Failure** | 12 (0.3%) | 3 (0.2%) | 9 (0.5%) |
| **Atrial Arrhythmias** | | | |
| **Arrhythmia Atrial** | 3 (<0.1%) | 0 (0%) | 1 (<0.1%) |
| **Bradycardia** | 3 (<0.1%) | 0 (0%) | 1 (<0.1%) |
| **Fibrillation Atrial** | 17 (0.4%) | 4 (0.2%) | 6 (0.3%) |
| **Tachycardia Supraventricular** | 3 (<0.1%) | 0 (0%) | 1 (<0.1%) |
| **Angina** | | | |
| **Unstable Angina** | 10 (0.3%) | 4 (0.2%) | 2 (0.1%) |
| **Angina Pectoris** | 22 (0.6%) | 10 (0.5%) | 12 (0.6%) |
| **Coronary Artery Disorder** | 25 (0.6%) | 7 (0.4%) | 6 (0.3%) |
| **Combined Anginal AEs[c]** | 57 (1.4%) | 21 (1.0%) | 20 (1.0%) |
| **Myocardial Ischemia** | 2 (<0.1%) | 2 (0.1%) | 0 (0%) |
| **Myocardial Infarction** | 19 (0.5%) | 5 (0.3%) | 9 (0.5%) |
| **Palpitations** | 23 (0.6%) | 7 (0.4%) | 8 (0.4%) |
| **Syncope** | 14 (0.4%) | 11 (0.6%) | 7 (0.4%) |
| **Thrombophlebitis** | | | |
| **Thrombophlebitis, Deep** | 12 (0.3%) | 5 (0.3%) | 1 (<0.1%) |
| **Thrombophlebitis, Combined[d]** | 17 (0.43%) | 8 (0.40%) | 5 (0.25%) |
| **Vasculitis** | 2 (<0.1%) | 1 (<0.1%) | 1 (<0.1%) |
| **Hypertension** | 78 (2.0%) | 40 (2.0%) | 61 (3.1%) |
| **Hypertension Aggravated** | 32 (0.8%) | 12 (0.6%) | 24 (1.2%) |

a. 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.

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**2.1c Reported Renal and Cardiac Adverse Events (cont)**

The next table summarizes selected cardiac adverse events according to the use of ASA. As expected, the patients taking ASA had a higher incidence of cardiac ischemic events in all three groups (they could be receiving ASA following a cardiac event like an MI). The combined rate of anginal disorders was numerically higher in the celecoxib treatment group for both ASA-using and non-ASA-using patients, compared with diclofenac and ibuprofen. In the patients not receiving ASA, the rate of Myocardial Infarction was also highest in the celecoxib group (0.2%) compared with the other two drugs (0.1%). Patients taking celecoxib but not ASA also had a greater than 2X greater incidence of atrial fibrillation than patients taking the comparator drugs. Of interest, patients who took ASA did not have an increased rate of hypertension or edema reported.

**Table 2.1c.4 Selected Cardiac Adverse Events Reported During CLASS According to ASA Use [a].**

| Adverse Events (AEs) | Celecoxib | Diclofenac | Ibuprofen |
|---|---|---|---|
| *ASA-Users* | 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%) |
| Atrial Arrhythmias | | | |
| Arrhythmia Atrial | 3 (0.3%) | 0 (0%) | 1 (0.2%) |
| Fibrillation Atrial | 8 (0.9%) | 2 (0.4%) | 4 (1.0%) |
| Tachycardia Supraventricular | 1 (0.1%) | 0 (0%) | 0 (0%) |
| 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 AEs[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%) |
| *Non-ASA Users* | 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%) |
| Atrial Arrhythmias | | | |
| Arrhythmia Atrial | 0 (0%) | 0 (0%0 | 0 (0%) |
| Bradycardia | 3 (<0.1%) | 0 (0%) | 1 (<0.2%) |
| Fibrillation Atrial | 9 (0.3%) | 2 (0.1%) | 2 (0.1%) |
| Tachycardia Supraventricular | 2 (<0.1%) | 0 (0%) | 1 (0.1%) |
| 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 (0.7%) | 6 (0.4%) | 8 (0.5%) |
| 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%) |

a. 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.

**2.1d Cardiac and Renal Adverse Events Causing Discontinuation**

Selected renal and cardiac adverse events leading to discontinuation are summarized below. Discontinuations for these events were rare and occurred equally in the three treatment groups. Of note, discontinuations for thrombotic cardiac events were not significantly different in the three groups.

**Table 2.1d.1 Renal and Cardiac Adverse Events Leading to Discontinuation During CLASS [a].**

| Adverse Event | Celecoxib 400 mg BID n=3987 | Diclofenac 75 mg BID n=1996 | Ibuprofen 800 mg TID n=1985 |
|---|---|---|---|
| **Renal** | | | |
| **Hypertension** | 10 (0.3%) | 3 (0.2%) | 5 (0.3%) |
| **Edema, peripheral** | 21 (0.5%) | 6 (0.3%) | 15 (0.8%) |
| **BUN Increased** | 13 (0.3%) | 10 (0.5%) | 3 (0.2%) |
| **Uremia** | 1 (<0.1%) | 0 (0%) | 0 (0%) |
| **Acute Renal Failure** | 0 (0%) | 1 (<0.1%) | 0 (0%) |
| **Cardiac** | | | |
| **Cardiac failure** | 4 (0.1%) | 1 (<0.1%) | 5 (0.3%) |
| **Myocardial Infarction** | 9 (0.2%) | 2 (0.1%) | 7 (0.4%) |
| **Cardiac Arrest** | 1 (<0.1%) | 4 (0.2%) | 1 (<0.1%) |
| **Combined Anginal Disorders[b]** | 12 (0.3%) | 5 (0.3%) | 5 (0.3%) |
| **Combined Thrombophlebitis[c]** | 6 (0.2%) | 3 (0.2%) | 2 (0.1%) |

a. Data from electronic submission, NDA 20-998 supplement S-009, Table T42.1.

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

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

There were no reported withdrawals for acidosis or reduced serum bicarbonate.

**2.1e Changes in Laboratory Parameters and Special Measurements**

The sponsor routinely collected laboratory and blood pressure data during the trial, as summarized in section 2.0b above. The first section below relates to the changes in laboratory measures during the trial. These changes can be analyzed in several different ways, falling into two general groups: analysis of mean changes and analysis of extreme individual changes. The first part will be concerned with the mean changes.

**Mean Changes from Baseline**

1. Changes in blood Urea Nitrogen (BUN) and Serum Creatinine (SCrt)

No clinically relevant differences between the three treatment groups were seen at any time point for the changes in mean BUN or SCrt. The reported differences, some of which achieved nominal statistical significance, were quite small and not clinically-relevant. For example, at 26 weeks the increase in mean SCrt was 2.1 for celecoxib and 4.2 U/L ($p<0.001$ per sponsor). This difference or 2.1 U/L is the same as a difference of 0.02 mg/dl (see Table 44.1 in electronic submission for details).

This conclusion was not altered when the populations that took ASA or not were examined separately (data not shown).

2. Changes in potassium, phosphate, bicarbonate, chloride

Similar to the changes observed for BUN and Crt, while there were numerical differences that achieved nominal statistical significance, none of there were of clinical significance (see table T44.1 for details).

This conclusion was not altered when the populations that took ASA or not were examined separately.

**2.1e Changes in Laboratory Parameters and Special Measurements (cont)**

**Extreme Changes from Baseline**

The table below summarizes the incidence of extreme laboratory values at any time during the course of the study after the baseline values for the three study groups. These analyses are derived from patients with a normal lab values at baseline. While there are differences between the study groups for individual measurements, overall the lab extremes occurred at more or less similar rates in the three treatments groups. Examples of this variability include:

1. Increases in serum $K^+$ occurred more frequently in patients taking celecoxib. This finding reinforces the observed increased rate of clinical adverse events associated with celecoxib use (see table 2.1c.1 above).

2. Decreased serum $HCO_3$ occurred more frequently in patients taking ibuprofen.

3. Increased serum creatinine (to ≥1.5 mg/dl) occurred more frequently in both ibuprofen and diclofenac, when compared with celecoxib. Additional analyses related to changes in serum creatinine appear below.

**Table 2.1e.1 Extreme Laboratory Values from Entire Study Period in CLASS [a].**

| Lab Test | Celecoxib 400 mg BID | Diclofenac 75 mg BID | Ibuprofen 800 mg TID |
|---|---|---|---|
| **BUN (mmol/l)** | | | |
| >7.1 | 1281/3141 (40.8%) | 549/1552 (35.4%)* | 510/1539 (33.3%)* |
| >14.3[d] | 31/3692 (0.8%) | 20/1849 (1.1%) | 16/1786 (0.9%) |
| **Creatinine (mmol/l)** | | | |
| >133[c] | 41/3684 (1.1%) | 37/1848 (2.0%)* | 30/1786 (1.7%)* |
| >265.2[c] | 1/3692 (<0.1%) | 0/1850 (0%) | 0/1786 (0%) |
| **Potassium (meq/l)** | | | |
| <3.5 | 89/3670 (2.4%) | 46/1836 (2.5%) | 116/1766 (6.6%)* |
| <3.0 | 7/3673 ((0.2%) | 7/1837 (0.4%) | 11/1770 (0.6%)* |
| >5.0 | 406/3654 (11.1%) | 182/1825 (10.0%) | 119/1758 (6.8%)* |
| >6.0 | 11/3673 (0.3%) | 3/1837 (0.2%) | 0/1770 (0%)* |
| **Chloride (mmol/l)** | | | |
| <75 | 0/3690 (0%) | 0/1847 (0%) | 0/1786 (0%) |
| <90 | 7/3690 (0.2%) | 1/1847 (<0.1%) | 4/1786 90.2%) |
| >110 | 86/3690 (2.3%) | 28/1847 (1.5%)* | 51/1785 (2.9%) |
| >120 | 0/3690 (0%) | 0/1847 (0%) | 0/1786 (0%) |
| **Bicarbonate (mmol/l)** | | | |
| <20 | 44/3687 (1.2%) | 22/1844 (1.2%) | 34/1782 (1.9%)* |
| <15 | 1/3689 (<0.1%) | 2/1844 (0.1%) | 0/1782 (0%) |
| >35 | 13/3689 (0.4%) | 7/1844 (0.4%) | 1/1782 (0.2%) |
| **Phosphate (mmol/l)** | | | |
| <0.32 | 0/3676 (0%) | 0/1841 (0%) | 0/1771 (0%) |
| <0.64 | 19/3676 (0.5%) | 16/1841 (0.9%) | 15/1771 (0.8%) |
| <0.96 | 791/3572 (22.1%) | 471/1775 (26.5%)* | 399/1705 (23.3%) |
| >2.10 | 0/3676 (0%) | 1/1841 (<0.1%) | 1/1771 (<0.1%) |
| >2.42 | 0/3676 (0%) | 0/1841 (0%) | 1/1771 (<0.1%) |

a. Data from electronic submission table T45.1 and at request of reviewer.
b. * values differ from celecoxib at p<0.05 per sponsor.
c. Corresponds to a serum creatinine of 1.5 and 3.0 mg/dl respectively.
d. Corresponds to a BUN of 20 and 40 mg/dl respectively.

These analyses were done according to the use of ASA and, for the most part, mirror the combined analysis. Of interest, the incidence of hyperkalemia (>5.0 meq/dl) and the incidence of elevated BUN (>20 and >40 mg/dl) were higher in all three groups when concomitant ASA was used. Hypokalemia was more common in the group who did not receive ASA.

## 2.1e Changes in Laboratory Parameters and Special Measurements (cont)

**Table 2.1e.2 Extreme Laboratory Values from Entire CLASS Study Period By ASA Use [a].**

| Lab Test | Celecoxib 400 mg BID | | Diclofenac 75 mg BID | | Ibuprofen 800 mg TID | |
|---|---|---|---|---|---|---|
| | ASA | No ASA | ASA | No ASA | ASA | No ASA |
| **BUN (mmol/l)** | | | | | | |
| **>7.1[d]** | 28/368 (7.6%) | 100/2483 (40.3%) | 117/322 (36.3%) | 432/1230 (35.1%)* | 115/312 (36.9%) | 398/1227 (32.4%)* |
| **>14.3[d]** | 12/829 (1.4%) | 0/2863 (0%) | 9/421 (2.1%) | 0/1428 (0%) | 5/386 (1.3%) | 0/1400 (0%) |
| **Creatinine (mmol/l)** | | | | | | |
| **>133[c]** | 9/826 (1.1%) | 32/2858 (1.1%) | 14/421 (3.3%)* | 23/1427 (1.6%) | 10/386 (2.6%) | 20/1400 (1.4%) |
| **>265.2[c]** | 1/829 (0.1%) | 0/2864 (0%) | 0/422 (0%) | 0/1428 (0%) | 0/386 (0%) | 0/1400 (0%) |
| **Potassium (meq/l)** | | | | | | |
| **>6.5** | 10/824 (1.2%) | 59/2846 (2.8%) | 9/419 (2.2%) | 37/1417 (2.6%) | 20/383 (5.2%)* | 96/1383 (6.9%)* |
| **<3.0** | 0/824 (0%) | 7/2849 (0.2%) | 1/420 (0.2%) | 6/1417 (0.4%) | 3/383 (0.8%) | 8/1387 (0.6%) |
| **<2.0** | 92/820 (11.2%) | 311/2837 (11.0%) | 56/416 (13.5%) | 126/1409 (8.9%)* | 40/383 (10.4%) | 159/1375 (11.7%) |
| **>6.0** | 0/824 (0%) | 11/2849 (0.4%) | 1/420 (0.2%) | 2/1417 (0.1%) | 0/383 (0%) | 0.1387 (0%) |
| **Chloride (mmol/l)** | | | | | | |
| **<75** | 0/829 (0%) | 0/2861 (0%) | 0/422 (0%) | 0/1425 (0%) | 0/386 (0%) | 0/1400 (0%) |
| **<90** | 0/829 (0%) | 7/2861 (0.2%) | 0/422 (0%) | 1/1425 (<0.1%) | 1/386 (0.3%) | 3/1400 (0.3%) |
| **>110** | 25/829 (3.0%) | 61/2861 (2.1%) | 6/422 (1.4%) | 22/1425 (1.5%) | 14/385 (3.6%) | 37/1400 (2.6%) |
| **>120** | 0/829 (0%) | 0/2861 (0%) | 0/422 (0%) | 0/1425 (0%) | 0/386 (0%) | 0/1400 (0%) |
| **Bicarbonate (mmol/l)** | | | | | | |
| **<20** | 8/829 (1.0%) | 36/2858 (1.3%) | 4/421 (1.0%) | 18/1423 (1.3%) | 10/385 (2.6%)* | 24/1397 (1.7%) |
| **<15** | 0/829 (0%) | 1/2860 (<0.1%) | 1/421 (0.2%) | 1/1423 (<0.1%) | 0/385 (0%) | 0/1397 (0%) |
| **>35** | 5/829 (0.6%) | 8/2860 (0.3%) | 1/421 (0.2%) | 6/1423 (0.4%) | 0/385 (0%) | 3/1397 (0.2%) |
| **Phosphate (mmol/l)** | | | | | | |
| **<0.32** | 0/824 (0%) | 0/2852 (0%) | 0/421 (0%) | 0/1420 (0%) | 0/383 (0%) | 0/1388 (0%) |
| **<0.64** | 3/824 (0.4%) | 16/2852 (0.6%) | 4/421 (1.0%) | 12/1420 (0.8%) | 2/383 (0.5%) | 13/1388 (0.9%) |
| **<0.96** | 171/796 (21.5%) | 620/2776 (22.3%) | 102/407 (25.1%) | 369/1368 (27.0%)* | 80/367 (21.8%) | 319/1342 (23.8%) |
| **>2.10** | 0/824 (0%) | 0/2852 (0%) | 0/421 (0%) | 1/1420 (<0.1%) | 0/383 (0%) | 1/1388 (<0.1%) |
| **>2.42** | 0/824 (0%) | 0/2852 (0%) | 0/421 (0%) | 0/1420 (0%) | 0/383 (0%) | 1/1388 (<0.1%) |

a. Data from electronic submission appendix 2.11.2.1 and 2.11.2.2 and at request of reviewer. Shown are maximum values from any time during trial relative to baseline.

b. * values differ from celecoxib at $p<0.05$ per sponsor.

c. Corresponds to a serum creatinine of 1.5 and 3.0 mg/dl respectively.

d. Corresponds to a BUN of 20 and 40 mg/dl respectively.

Because of the important interaction between changes in BUN and serum creatinine (SCrt) the incidence of the development of combined abnormalities of these two lab measurements in patients with normal BUN and creatinine at baseline was examined (shown below). In this analysis, celecoxib use was not associated with an increased rate of renal injury.

**Table 2.1e.3 Incidence of Combined Abnormalities in BUN and SCrt in CLASS [a, b].**

| Parameter | Celecoxib 400 mg BID | Diclofenac 75 mg BID | Ibuprofen 800 mg TID |
|---|---|---|---|
| **BUN ≥14.3 mmol/l and SCrt ≥159 mmol/l[c]** | 4 (0.1%) | 1 (<0.1%) | 5 (0.3%) |
| **BUN ≥7.1 and SCrt > 133 mmol/l[d]** | 50/3702 (1.4%) | 43/1852 (2.3%)* | 32/1807 (1.8%) |

a. Data from electronic datasets table T48 and at request of reviewer from sponsor. Patients with normal renal function at baseline.

b. SCrt = serum creatinine.

c. Corresponds to a BUN/Crt of 40/3.0 mg/dl.

d. Corresponds to a BUN/Crt of 20/1.5 mg/dl.

**2.1e Changes in Laboratory Parameters and Special Measurements (cont)**

These same data, grouped according to ASA use, appear below. For mild increases in BUN and SCrt, the rate were lowest in the celecoxib group overall, regardless of the use of ASA.

**Table 2.1e.4 Incidence of Combined Abnormalities in BUN and SCrt in CLASS Grouped by ASA Use [a, b].**

| Parameter | Celecoxib 400 mg BID | | Diclofenac 75 mg BID | | Ibuprofen 800 mg TID | |
|---|---|---|---|---|---|---|
| | ASA | NoASA | ASA | NoASA | ASA | NoASA |
| BUN ≥14.3 mmol/l and SCrt ≥159 mmol/l[c] | 5/834 (0.6%) | 9/2868 (0.3%) | 1/423 (0.2%) | 5/1429 (0.4%) | 3/390 (0.8%) | 4/1417 (0.3%) |
| BUN ≥7.1 mmol/l and SCrt ≥103 mmol/l[d] | 12/834 (1.4%) | 38/2868 (1.3%) | 17/423 (4.0%) | 26/1429 (1.8%) | 11/390 (2.8%) | 21/1417 (1.5%) |

a. Data at request of reviewer from sponsor. Based on patients with normal renal function at baseline.
b. SCrt = serum creatinine.
c. Corresponds to a BUN/Crt of 40/3.0 mg/dl.
d. Corresponds to a BUN/Crt of 20/1.5 mg/dl.

**2.1f Changes in Blood Pressure**

In the original NDA submission database, celecoxib use was associated with increased hypertension when compared with placebo (as commonly seen for NSAIDs). The sponsor analyzed the changes in blood pressure (BP) recorded for those subjects in CLASS with both baseline and at least one follow-up BP reading. The changes in the mean BP for the three treatment groups hovered around 0 for the trial and were of little clinical significance. The incidence of abnormal elevations in BP is summarized below. No clinically-significant differences between the treatment groups were apparent. Similar findings were seen when the patients were grouped according to ASA use (not shown).

**Table 2.1f.1 Incidence of BP Elevations During CLASS [a].**

| Parameter | Celecoxib 400 mg BID | Diclofenac 75 mg BID | Ibuprofen 800 mg TID |
|---|---|---|---|
| **Sitting Systolic BP ≥15% increase over baseline at final visit** | | | |
| All Patients | 315/2925 (10.8%) | 163/1434 (11.4%) | 173/1387 (12.5%) |
| ASA Users | 82/653 (12.6%) | 38/327 (11.6%) | 39/287 (13.6%) |
| Non-ASA Users | 233/2272 (10.3%) | 125/1107 (11.3%) | 134/1100 (12.2%) |
| **Sitting Diastolic BP ≥15% increase over baseline at final visit** | | | |
| All Patients | 298/2925 (10.2%) | 146/1434 (10.2%) | 134/1387 (9.7%) |
| ASA Users | 70/63 (10.7%) | 33/327 (10.1%) | 30/287 (10.5%) |
| Non-ASA Users | 228/2272 (10.0%) | 113/1107 (10.2%) | 104/1100 (9.5%) |

a. Data from electronic submission Table T54 and from sponsor at reviewer's request.

## 3.0 SUMMARY

The Celecoxib Long-Term Arthritis Safety Study (CLASS) compared the effects of three anti-inflammatory drugs in a population of patients with osteoarthritis: celecoxib, diclofenac, and ibuprofen. The majority of patients did not receive aspirin (ASA), although around 20% of the patients received ASA and were available for separate analysis. The aspects of the safety database from CLASS to be commented on in this consultation are focused on the comparative renal and cardiac effects of celecoxib, diclofenac and ibuprofen.

### 3.1 Comparative Effects of Celecoxib, Diclofenac and Ibuprofen on Acid-Base Balance

In the original celecoxib NDA database, serum bicarbonate ($HCO_3$) levels were not measured. In the NDA there was an association between celecoxib use and an increase in serum chloride, which can be interpreted as related to fall in serum $HCO_3$. To address if celecoxib affected acid-base balance, the sponsor measured changes in serum $HCO_3$ in CLASS and collected adverse events related to changes in systemic acid-base balance. The data above support the following conclusions:

1) Between 1 and 2% of the subjects in all three treatment groups had a measured $HCO_3$ <20 meq/dl during the study after starting with a normal baseline >25 mg/dl. The rate for celecoxib, however, was the same as for diclofenac and less than celecoxib (Table 2.1e.1).

2) There was no increase in reported clinical adverse events related to changes in acid-base balance in the celecoxib group: such adverse events were quite rare in the database for all three drugs (Tables 2.1b.1 and 2.1c.1).

3) Finally, bony fractures, as a marker for chronic metabolic acidosis, occurred at equal rates in the three treatment groups (Tables 2.1c.1 and 2.1c.2).

**Conclusion Regarding Acid-Base Balance**

Overall, then, celecoxib, diclofenac and ibuprofen use are uncommonly associated with changes in acid-base balance. Such effects may be mediated by the inhibition of COX-1 and COX-2 known to be expressed in the kidney. In CLASS celecoxib, diclofenac and ibuprofen had similar overall effects on acid-base balance.

### 3.2 Comparative Incidence of Renal Adverse Effects for Celecoxib, Diclofenac and Ibuprofen

The use of NSAIDs has been associated with several severe forms of renal injury including Nephrotic Syndrome and acute renal failure leading to uremia. In addition, NSAID use has been associated with asymptomatic increases in serum creatinine and BUN (see references at end of consult for details). There is uncertainty about the exact incidence of these changes following long-term NSAID use, with estimates ranging from 1:100 to <1:1000. Less severe renal injury was assessed in two ways in CLASS: clinical events reported as adverse events and changes in serum markers of renal injury (BUN/ creatinine) from routine blood draws performed during the trial. The data from CLASS support the following conclusions regarding the occurrence of renal adverse events in the population studied:

**Renal Serious Adverse Events**

1) The rate of severe renal injury during therapy with celecoxib, diclofenac or ibuprofen was very low, with no reported cases of Nephrotic Syndrome or life-threatening hyperkalemia, and one case of uremia (table 2.1b.1).

**Renal Adverse Events**

2) Less severe clinical renal adverse events were reported in a small percentage of the population (table 2.1c.1).

3) Hyperkalemia was more commonly reported as an adverse event in the patients receiving celecoxib, while hypokalemia was more commonly reported in the patients receiving NSAIDs (table 2.1c.1).

4) BUN increase was more commonly reported as an adverse event in the diclofenac group (table 2.1c.1).

5) Edema as an adverse event was reported in 3-5 % of the population, and was reported with equal frequency in the celecoxib and ibuprofen treatment groups (3-4%). A higher incidence of edema was reported in the ibuprofen group (5-6%) (table 2.1c.3).

**3.2 Comparative Incidence of Renal Adverse Effects for Celecoxib, Diclofenac and Ibuprofen (cont)**

**Renal Adverse Events (cont)**

6) Hypertension as an adverse event was reported less in the celecoxib group (2.7%) than in the diclofenac (3.1%) or ibuprofen (4.6%) groups (table 2.1c.4). Changes in Blood Pressure (BP) were analyzed for those subjects with more than one reading during the trial (section 2.1f). The incidence of significant increases in systolic or diastolic BP above baseline were relatively common (10-15%), but occurred equally in all three treatment groups (table 2.1f.1).

7) As urinalyses were not routinely collected no conclusions can be reached about the comparative effects of the three drugs on urinary protein. Hematuria was reported uncommonly in all three treatment groups (table 2.1c.1).

**Laboratory Adverse Events**

8) Small changes in mean chemistries were reported that are of little clinical significance (section 2.1e).

9) Large individual changes from baseline were uncommon in all three treatment groups, making it difficult to attribute observed differences to individual drug effects (table 2.1e.1).

10) Increases in serum potassium to >5.0 and >6.0 meq/l occurred more frequently in patients receiving celecoxib than for either diclofenac or ibuprofen. The differance between the rate of $K^+$ >5.0 for celecoxib (11.1%) and ibuprofen (6.8%) achieved nominal statistical significance (table 2.1e.1).

11) Increases in BUN to >20 mg/dl were more common in the celecoxib group (40.8%) than in the diclofenac (35.4%) or ibuprofen (33.3%) groups. However, the rate of increased serum creatinine to >1.5 mg/dl was higher in the diclofenac group (2.0%) when compared with celecoxib (1.1%). The latter difference achieved nominal statistical significance.

12) The incidence of combined abnormalities in BUN and creatinine was also analyzed. The rates for these combined endpoints, starting from a normal baselin, were lowest in the celecoxib group, regardless of the concomitant use of ASA (tables 2.1e.3 and 2.1e.4). For example, the percentage of patients with a BUN> 20 mg/dl and creatinine >1.5 mg/dl was lowest in the celecoxib group (1.4%) when compared with ibuprofen (1.8%) or diclofenac (2.3%).

**Effect of ASA Use on Renal Adverse Events**

Given that use of ASA in this population would indicate a higher level of pre-existing cardiovascular disease, interpretation of adverse events according to the use of ASA is difficult. The following differences were seen in the CLASS database analysis according to the use of ASA:

13) Increases in BUN were reported more commonly (approximately 3X more common) in the group treated with ASA and any one of the three NSAIDs (table 2.1c.2).

14) Too few severe clinical renal events (renal failure, uremia, nephrotic syndrome) occurred for analysis. Hypertension was more commonly reported as an adverse event in patients taking ASA (table 2.1c.4).

15) For adverse events related to laboratory measurements, decreases in serum phosphate and increases in serum potassium, BUN or creatinine were more commonly seen in patients who took ASA along with one of the three NSAIDs (table 2.1e.2). In particular, the increased incidence of serum $K^+$ >5.0 and BUN >20 mg/dl in patients taking ASA achieved nominal statistical signficance.

16) For adverse events related to laboratory measurements, decreases in serum potassium occurred more commonly in patients not taking ASA (table 2.1e.2).

17) The incidence of combined abnormalities in BUN and creatinine was analyzed. The rates for these combined endpoints were lowest in the celecoxib group, regardless of the concomitant use of ASA (tables 2.1e.3 and 2.1e.4).

**3.2 Comparative Incidence of Renal Adverse Effects for Celecoxib, Diclofenac and Ibuprofen (cont)**

**Conclusion Regarding Renal Effects of Celecoxib, Diclofenac and Ibuprofen**

Serious renal adverse event linked to the three NSAIDs used in the study were rare (occurring at less than 1:1000 patient-years of exposure. For the less severe renal adverse effects, no clear differences were seen between celecoxib and the two NSAIDs, although there were differences between celecoxib and one of the NSAIDs for some adverse events. In particular, worsened hypertension and worsened edema were not clearly less frequent with celecoxib when compared with both diclofenac and ibuprofen. There was a tendency for more hyperkalemia in patients treated with celecoxib compared with both NSAIDs, but this effect occurred in a small fraction of the patients and was not associated with an increased rate of severe hyperkalemia. Additionally, worsened hypertension appeared to be more common in patients who took ASA. There was also a trend towards fewer combined increases in serum creatinine and BUN in the celecoxib group, but the clinical significance of this difference is not clear. In the CLASS study, the pattern of renal adverse events for celecoxib was not distinguished from that of NSAIDs (as typified by diclofenac and ibuprofen).

**3.3 Comparative Incidence of Cardiac Adverse Effects for Celecoxib, Diclofenac and Ibuprofen**

NSAIDs have been reported to have a variety of cardiovascular effects, including worsening hypertension and edema (see above). Recently, particular concern has been raised regarding a possible pro-thrombotic effect of selective inhibition of COX-2 (for example, by celecoxib). The data from the CLASS trial support the following conclusions about the cardiac effects of celecoxib, diclofenac and ibuprofen:

**Cardiac Serious Adverse Events and Mortality**

1) While the long-term data from the original celecoxib NDA suggested a dose-dependent effect on cardiac mortality (table 2.1a.1), the rates for total and cardiovascular mortality were similar in the CLASS trial celecoxib, diclofenac and ibuprofen (table 2.1a.2). This conclusion was not altered when the patients were divided according to their use of ASA (table 2.1a.3).

2) Reported serious adverse events (SAEs) were infrequent to rare in the CLASS trial (table 2.1b.1). The rate of "Combined Anginal AEs", was higher in the celecoxib group when compared with diclofenac or ibuprofen. This pattern was independent of the concomitant use of ASA (table 2.1b.2). For myocardial infarctions, there were 32 events reported as SAEs in the trial population as a whole, and the rates were 0.8%, 0.4% and 0.8% for celecoxib, diclofenac and ibuprofen respectively.

3) Reported SAEs for "Combined Atrial Arrhythmias" were infrequent, but occurred most frequently in the celecoxib group (0.6%) than in the diclofenac (0.2%) or ibuprofen (0.4%) groups (table 2.1b.1). For patients not taking ASA, incidence for these same groups was 1.7%, 0.1% and 0% respectively (table 2.1b.2).

**Cardiac Adverse Events**

4) Ischemic cardiac events were reported in <1% of the population of CLASS. For the '"Combined Anginal AEs" the rate for the celecoxib group (1.4%) was higher than the diclofenac or ibuprofen groups (1.0%). Myocardial infarctions were reported as adverse events in 33 patients in total (out of 7968 patients enrolled): 19 (0.5%) with celecoxib, 5 (0.3%) with diclofenac, and 9 (0.5%) with ibuprofen (table 2.1c.3).

5) Atrial arrhythmias reported as AEs occurred more frequently in the celecoxib group than in either of the comparator drug groups (table. 2.1c.3).

6) Heart failure reported as AEs occurred at similar rates in the three treatment groups (0.2 to 0.5%) (table 2.1c.3).

**Effect of ASA Use on Cardiac Adverse Events**

7) When the cardiac deaths were divided according to the use of ASA, the mortality rates for celecoxib, diclofenac and ibuprofen were similar, although each category had few events (table 2.1a.3). For example, among the 13 deaths in patients not taking ASA, the mortality rates for celecoxib, diclofenac and ibuprofen were 0.3%, 0.6%, and 0.2% respectively.

8) For serious adverse events (SAEs), the rate of ischemic cardiac events was highest in the celecoxib group for the "Combined Anginal SAEs," "Combined Atrial SAEs" and " Myocardial Infarctions" (table 2.1b.2).

### 3.3 Comparative Incidence of Cardiac Adverse Effects for Celecoxib, Diclofenac and Ibuprofen

**Conclusion Regarding Cardiac Effects of Celecoxib, Diclofenac and Ibuprofen**

The CLASS trial data do not support a large 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 pro-thrombotic effect of celecoxib, such as might be reflected in the relative rates of cardiac adverse events related to ischemia.

The observed differences in the rates of atrial arrhythmias are derived from small numbers of patients and lack supportive evidence from other sources ( *e.g.*, animal models, post-marketing data) and their clinical relevance cannot be determined.

In the CLASS trial, the cardiac adverse event profile for celecoxib was not clearly different from that of NSAIDs (as represented by diclofenac and ibuprofen).

## 4.0 CONCLUSIONS/ RECOMMENDATIONS

The CLASS trial exposed subjects with osteoarthritis and rheumatoid arthritis to one of the three study drugs for varying periods of time, including approximately 2300 patients treated with celecoxib, 1100 patients treated with diclofenac and 1000 patients treated with ibuprofen for ≥6 months. Two issues are relevant to this consult: the effect of celecoxib on acid-base balance and the relative rates of renal and cardiac adverse events see in the CLASS trial. The data analyzed above support the following conclusions related to these three issues:

1. The CLASS database contains no evidence for an adverse effect of celecoxib on acid-base balance relative to either diclofenac or ibuprofen.
2. The CLASS database does not support a large 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 pro-thrombotic effect of celecoxib, reflected in the relative rates of cardiac adverse events related to ischemia. Detecting such an effect would require a much larger database than CLASS.
3. In the CLASS database the cardiac and renal adverse event profiles for celecoxib were not clearly different from that of NSAIDs (as represented by diclofenac and ibuprofen). This includes adverse events reported by investigators ( *e.g.*, worsened hypertension or edema, uremia) and those detected through routine laboratory or blood pressure measurements ( *e.g.*, increased BUN/ Crt or systolic blood pressure).
4. The data suggesting an increased rate of supraventricular arrhythmias in patients taking celecoxib compared to diclofenac and ibuprofen are provocative but require additional investigation.
5. 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.
6. A lack of information about specific use of ASA in CLASS limits the interpretation of analyses done with and without ASA use. No clear clinical effect of concomitant use of ASA with celecoxib, diclofenac or ibuprofen was identified, although worsened hypertension was more somwhat more common when ASA was used by patients taking any of the three drugs.
7. Additional analyses are needed to address the generalizability of the results from CLASS and other large clinical trials using NSAIDs to the use of NSAIDs in the general population.

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# OPDRA Review

## US Deaths related to GI Bleeding, Obstruction, Peforation, or Stenosis