Table 5.1.4.1.6 Shift in urine lab values in the 12-week, controlled North American Arthritis trials of celecoxib from NDA 20-998[a].

| Maximal Change in Urine Lab Value | Placebo | Celecoxib 400 mg BID | Active Controls |
|---|---|---|---|
| **Urine Protein**<br>High (trace to 1+) | 11/395 from Normal<br>0/8 from High<br>0/8 from Extreme High | 10/389 from Normal<br>2/11 from High<br>0/5 from Extreme High | 16/409 from Normal<br>1/8 from High<br>0/3 from Extreme High |
| Extreme High (above limit of 1+) | 5/395 from Normal<br>2/8 from High<br>6/8 from Extreme High | 5/389 from Normal<br>0/11 from High<br>2/5 from Extreme High | 3/409 from Normal<br>0/8 from High<br>2/3 from Extreme High |
| **Urine Glucose**<br>High (trace to 1+) | 3/405 from Normal<br>0/2 from High<br>0/4 from Extreme High | 2/396 from Normal<br>0/4 from High<br>0/5 from Extreme High | 0/412 from Normal<br>0/1 from High<br>1/7 from Extremely High |
| Extreme High (above limit of 1+) | 6/405 from Normal<br>1/2 from High<br>2/4 from Extreme High | 7/396 from Normal<br>2/4 from High<br>3/5 from Extreme High | 2/412 from Normal<br>0/1 from High<br>2/7 from Extreme High |
| **Urine RBCs**<br>High (5-10 per HPF) | 7/382 from Normal<br>0/9 from High<br>3/20 from Extreme High | 10/388 from Normal<br>0/6 from High<br>0/10 from Extreme High | 11/394 from Normal<br>0/12 from High<br>0/14 from Extreme High |
| Extreme High (>10 per HPF) | 17/382 from Normal<br>2/9 from High<br>8/20 from Extreme High | 24/388 from Normal<br>3/7 from High<br>2/10 from Extreme High | 15/394 from Normal<br>1/12 from High<br>5/14 from Extreme High |
| **Urine WBCs**<br>High (10-20 per HPF) | 10/ 383 from Normal<br>4/15 from High<br>3/13 from Extreme High | 12/390 from Normal<br>1/7 from High<br>1/8 from Extreme High | 13/402 from Normal<br>3/6 from High<br>3/12 from Extreme High |
| Extreme High (>20 per HPF) | 16/383 from Normal<br>4/15 from High<br>8/13 from Extreme High | 16/390 from Normal<br>2/7 from High<br>2/8 from Extreme High | 22/402 from Normal<br>0/6 from High<br>4/12 from Extreme High |

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

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A similar analysis was performed for the subjects in the long-term, open-label study.

Table 5.1.4.1.7 Incidence of extreme renal serum lab values in the open-label trial from NDA 20-998[a].

| Maximal Change in Lab Value | Celecoxib |
|---|---|
| **Creatinine (μmol/l)** | |
| High (176.8-265.2 mmol/l) | 5/4376 from Normal<br>0/0 from High<br>0/0 from Extreme High |
| Extreme high | 1/4376 from Normal<br>0/0 from High<br>0/0 from Extreme High |
| **BUN (mmol/l)** | |
| High (9.3-14.3 mmol/l) | 298/4251 from Normal<br>82/121 from High<br>1/4 from Extreme High |
| Extreme high | 5/4251 from Normal<br>7/121 from High<br>2/4 from Extreme High |
| **Sodium (mmol/l)** | |
| Low (120-135 mmol/l) | 109/173 from Low<br>395/3935 from Normal<br>1/89 from High |
| High (140-160 mmol/l) | 4/173 from low<br>346/3935 from Normal<br>29/89 from High |
| Extreme High or Low | None |
| **Potassium (mmol/l)** | |
| Low (2-3.5 mmol/l) | 48/91 from Low<br>174/3976 from Normal<br>0/119 from High |
| High (5-6 mmol/l) | 3/91 from Low<br>329/3976 from Normal<br>59/119 from High |
| Extreme High (>6 mmol/l) | 1/3976 from Normal<br>1/119 from Extreme High |
| **Chloride** | |
| Low (75-90 mmol/l) | 0/1 from Low<br>4/4027 from Normal<br>0/171 from High |
| High (90-110 mmol/l) | 599/4027 from Normal<br>60/171 from High |
| Extreme High or Low | None |
| **Phosphate** | |
| Low (0.32-0.97 mmol/l)<br>(1.0 to 3.0 mg/dl) | 466/643 from Low<br>1069/3538 from Normal<br>1/9 from High |
| High (1.61-2.42 mmol/l)<br>(5.0 to 7.5 mg/dl) | 2/643 from Low<br>68/3538 from Normal<br>2/9 from High |
| Extreme High or Low | None |

a. Data from NDA Integrated Safety Summary, table 5.4. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

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Table 5.1.4.1.8 Incidence of extreme urine lab values in the long-term, open-label trial from NDA 20-998[a].

| Maximal Change in Urine Lab Value | Celecoxib |
|---|---|
| **Urine Protein** High (trace to 1+) | 179/3970 from Normal<br>15/79 from High<br>5/37 from Extreme High |
| Extreme High (above limit of 1+) | 79/3970 from Normal<br>12/79 from High<br>22/37 from Extreme High |
| **Urine Glucose** High (trace to 1+) | 50/3989 from Normal<br>4/34 from High<br>1/63 from Extreme High |
| Extreme High (above limit of 1+) | 107/3989 from Normal<br>20/34 from High<br>54/63 from Extreme High |
| **Urine RBCs** High (5-10 per HPF) | 141/3926 from Normal<br>2/53 from High<br>9/108 from Extreme High |
| Extreme High (>10 per HPF) | 313/3926 from Normal<br>17/53 from High<br>47/108 from Extreme High |
| **Urine WBCs** High (10-20 per HPF) | 189/3892 from Normal<br>21/79 from High<br>17/116 from Extreme High |
| Extreme High (>20 per HPF) | 265/3892 from Normal<br>17/79 from High<br>60/116 from Extreme High |

a. Data from NDA Integrated Safety Summary, table 5.4. The database used is the is trials, including studies 012, 013, 020, 021, 023, 047, 054, 060, 062, 071, and 087.

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### 5.1.4.2 Special Investigations Related to Renal and Cardiac AEs

The sponsor investigated the association of several AEs related to renal and cardiac events as part of the NDA submission. Others were performed at the request of this reviewer. Overall, these were aimed at exploring potential patterns of renal or cardiac injury.

As will be discussed below, there is an apparent link between celecoxib (or active control) administration and an increased incidence of edema, when compared with placebo. This was especially true for 'peripheral edema' as described by the investigators (see also the listing of adverse events, table 5.1.3. above). The sponsor investigated the association of this increased edema with other renal and cardiovascular AEs.

First, few individuals developed both edema and had worsening of their hypertension (as marked by a 5 mm Hg increase in diastolic BP). There was a non-significant trend towards a larger group of such patients in the celecoxib population, as compared with placebo. There was no similar trend in the active control group. The shaded boxes represent a difference at a nominally significant level of <0.05.

Table 5.1.4.2.1 Occurrence of HTN and edema in the North American Arthritis trials[a].

| Syndrome | Placebo N=1136 | Celecoxib N=2690 | | Placebo N=1136 | Active Control N=1099 |
|---|---|---|---|---|---|
| **Adverse Events** | | | | | |
| **Any of the 4 AEs below** | 31 (1.7%) | **116 (3.3%)** | | 19 (1.7%) | **41 (3.7%)** |
| **HTN** | 5 (0.3%) | 22 (0.6%) | | 5 (0.4%) | 7 (0.6%) |
| **HTN Aggravated** | 7 (0.4%) | 20 (0.6%) | | 4 (0.4%) | 5 (0.5%) |
| **Edema, Generalized** | 0 (0%) | 4 (0.1%) | | 0 (0%) | **9 (0.8%)** |
| **Edema, Peripheral** | 12 (1.2%) | **52 (2.3%)** | | 12 (1.1%) | 21 (1.9%) |
| **Diastolic BP Rise[b]** | 35 (1.9%) | 87 (2.5%) | | 20 (1.8%) | 23 (2.1%) |
| **Both AE and Increased BP** | 2 (0.1%) | 11 (0.3%) | | 1 (<0.1%) | 0 (0%) |

a. Data from Integrated Safety Summary, table 31.3.4.
b. >95 mm Hg and >5 mm Hg from baseline).

Next, there was a trend towards an association between the development of edema and renal insufficiency.

Table 5.1.4.2.2 Occurrence of edema and renal insufficiency in the North American Arthritis trials[a].

| AEs, both clinical and lab | Placebo N=1864 | Celecoxib N=3512 | | Placebo N=1136 | Active Control N=1099 |
|---|---|---|---|---|---|
| **Edema, Generalized** | 0 (0%) | 4 (0.1%) | | 0 (0%) | **9 (0.8%)** |
| **Edema, Peripheral** | 12 (12%) | **52 (2.3%)** | | 12 (1.1%) | 21 (1.9%) |
| **BUN >14.3 mmol/l[b]** | 0 (0%) | 5 (0.2%) | | 0 (0%) | 2 (0.2%) |
| **Creatinine >159 mmol/l[c]** | 0 (0%) | 4 (0.2%) | | 0 (0%) | 0 (0%) |
| **Chloride >110 mmol/l** | 60 (3.2%) | **209 (6.0%)** | | 55 (4.8%) | **97 (8.8%)** |
| | | | | | |
| **Both AEs and Labs** | 0 (0%) | 4 (0.2%) | | 0 (0%) | 2 (0.2%) |

a. Data from corrected tables from the Integrated Safety Summary, table 3.1.3.6, dated 9.16.98.
b. 43 mg/dl.
c. 1.8 mg/dl.

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Next, the sponsor examined the association between weight gain and edema formation. Using only the subset of patients with both sets of data available, the sponsor reported that there was no association between weight gain and edema formation. Note that the incidence of edema in this table differs from that in the AE table above (5.1.3.1 and shown as top line in table below), where all reported incidence of edema (irregardless of the collection of weights) is included. Shaded boxes are nominally significant.

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

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

a. Data from corrected tables from the Integrated Safety Summary, table 3.1.3.6, dated 9.16.98. Edema includes only 100 and 200 mg dose groups.
b. Data from sponsor, only for those patients with both weight and edema AE data. Includes 50 to 400 mg doses.

In data not shown, there was no association between the development of edema and the development of hyponatremia or the development of urine protein >1+.

The sponsor also looked at the association between the presence of back pain and hematuria (as occurred following the administration of specific NSAIDs). For celecoxib, there was no trend towards such an association (data not shown). The reader is referred to the Integrated Safety Summary, tables 31.3.3-14 for details.

At the request of this reviewer, the sponsor also performed a series of analyses looking for associations between specific lab abnormalities and adverse events. The laboratory values and the AEs used for the analysis are first presented below, taken from the North American Arthritis trials and then Long-term open-label trial. A subset of the trials used in table 5.1.4.1.2 were used, including only those trials where celecoxib was directly compared with both active control and placebo, and where serum chloride was measured.

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Table 5.1.4.2.3 Incidence of selected AEs and lab abnormalities in the controlled U.S. arthritis trials.

| AE/ Lab Value | Placebo N=1136 | Celecoxib 100 mg N=1131 | Celecoxib 200 mg N=1125 | Celecoxib 400 mg N=434 | Active Control N=1099 |
|---|---|---|---|---|---|
| **Serum Labs** | | | | | |
| Chloride >110 mmol/l | 48 (4.2%) | 90 (8.0%) | 88 (7.8%) | 37 (8.5%) | 82 (7.5%) |
| Chloride >120 mmol/l | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| BUN >6.7 mmol/l[b] | 140 (12.3%) | 296 (26.2%) | 379 (33.7%) | 147 (33.9%) | 482 (43.9%) |
| BUN >14.3 mmol/l[c] | 0 (0%) | 1 (<0.1%) | 4 (0.4%) | 0 (0%) | 2 (0.2%) |
| Creatinine >132 μmol/l[d] | 6 (0.5%) | 7 (0.6%) | 15 (1.3%) | 2 (0.5)% | 14 (1.3%) |
| Creatinine >159 μmol/l[e] | 0 (0%) | 1 (<0.1%) | 3 (0.3%) | 0 (0%) | 0 (0%) |
| $PO_4$ <0.97 mmol/l[f] | 195 (17.2%) | 233 (20.6%) | 237 (21.1%) | 83 (19.1%) | 351 (31.9%) |
| $Ca^{2+}$ <1.7 mmol/l | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Urine Labs** | | | | | |
| Urine Glucose >trace | 30 (2.6%) | 46 (4.1%) | 34 (3.0%) | 13 (3.0%) | 22 (2.0%) |
| Urine Glucose >1+ | 21 (1.8%) | 36 (3.2%) | 26 (2.3%) | 11 (2.5%) | 17 (1.5%) |
| Urine Glucose >trace, Non-diabetics | 25 (2.4%) | 20 (2.0%) | 26 (2.5%) | 12 (3.0%) | 23 (2.3%) |
| Urine Protein >Trace | 43 (3.8%) | 41 (3.6%) | 44 (3.9%) | 15 (3.5%) | 48 (4.4%) |
| Urine pH >7.5 | 10 (0.9%) | 13 (1.1%) | 12 (1.1%) | 2 (0.5%) | 13 (1.3%) |
| **Adverse Events** | | | | | |
| Fracture, Accidental | 3 (0.3%) | 6 (0.5%) | 4 (0.4%) | 4 (0.9%) | 4 (0.4%) |
| Fracture, Pathological | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Myalgias | 23 (2.0%) | 24 (2.1%) | 21 (1.9%) | 6 (1.4%) | 8 (0.7%) |
| Osteoporosis | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

a. Data from data submitted to FDA 10.9.98 from sponsor, and not independently confirmed by FDA reviewer.
b. 20 mg/dl.
c. 40 mg/dl.
d. 1.5 mg/dl.
e. 1.8 mg/dl
f. 3.0 mg/dl.

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Similar data was summarized for the long-term, open-label trial.

Table 5.1.4.2.4 Incidence of selected AEs and lab abnormalities in the controlled U.S arthritis trials.

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| AE/ Lab Value | Celecoxib N=4499 |
|---|---|
| **Serum Labs** | |
| Chloride >110 mmol/l | 593 (13.2%) |
| Chloride >120 mmol/l | 0 (0%) |
| BUN >6.7 mmol/l[b] | 1995 (44.3%) |
| BUN >14.3 mmol/l[c] | 14 (0.3%) |
| Creatinine >132 μmol/l[d] | 53 (1.2%) |
| Creatinine >159 μmol/l[e] | 10 (0.2%) |
| $PO_4$ <0.97 mmol/l[f] | 1361 (30.3%) |
| $Ca^{2+}$ <1.7 mmol/l | 1 (<0.1%) |
| **Urine Labs** | |
| Urine Glucose >trace | 200 (4.4%) |
| Urine Glucose >1+ | 150 (3.3%) |
| Urine Protein >Trace | 274 (6.1%) |
| Urine pH >7.5 | 68 (1.5%) |
| Urine pH >8.5 | 6 (0.1%) |
| **Adverse Events** | |
| Fracture, Accidental | 63 (1.4%) |
| Fracture, Pathological | 5 (0.1%) |
| Myalgias | 14 (0.3%) |
| Osteoporosis | 113 (2.5%) |

a. Data from data submitted to FDA 10.9.98 from sponsor.
b. 20 mg/dl.
c. 40 mg/dl.
d. 1.5 mg/dl.
e. 1.8 mg/dl
f. 3.0 mg/dl.

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Using the abnormalities identified above, the sponsor performed a series of analyses searching for associations between one or more of these abnormalities. Shading indicates that the treatment group (either celecoxib or active control) differed significantly from placebo (nominal $p<0.05$).

1a. Association between hyperchloremia and abnormalities in serum BUN/ Crt/ PO4 and/or urine Glucose/ protein/ pH. Controlled Trials.

First, the sponsor looked for an association between hyperchloremia and other renal lab abnormalities. A significantly higher percentage of patients in the celecoxib and active control groups had hyperchloremia and one or more of these abnormalities. Note also that there was a significantly higher incidence of elevated BUN, and decreased $PO_4$ in the celecoxib and active control groups, relative to placebo. While there was a trend towards an increased incidence of glycosuria in the celecoxib group, the sponsor reports that if the diabetics are excluded from the analysis, this difference disappears.

Table 5.1.4.2.5 Hyperchloremia and other renal lab abnormalities in the controlled NA trials[a].

| Abnormality | Placebo N=1136 | Celecoxib N=2256 | Active Control N=1099 |
|---|---|---|---|
| **Chloride >110 mmol/l** | 60 (3.2%) | 209 (6.0%) | 97 (8.8%) |
| **BUN >6.7 mmol/l** | 140 (12.3%) | 675 (29.9%) | 482 (43.9%) |
| **Crt >132 mmol/l** | 6 (0.5%) | 22 (1.0%) | 14 (1.3%) |
| **PO4 <0.97 mmol/l** | 195 (17.2%) | 470 (20.8%) | 351 (31.9%) |
| **Urine Glucose >trace** | 30 (2.6%) | 80 (3.5%) | 22 (2.0%) |
| **Urine Protein >trace** | 43 (3.8%) | 85 (3.8%) | 48 (4.4%) |
| **Urine pH >7.5** | 10 (0.9%) | 25 (1.1%) | 14 (1.3%) |
| **Any of the above Lab Abnormalities** | 356 (31.3%) | 1084 (48.0%) | 702 (63.9%) |
| **Both Hyperchloremia and one or more other lab abnormality** | 27 (2.4%) | 95 (4.2%) | 65 (5.9%) |
| **Both Hyperchloremia and one or more other lab abnormality at last clinic visit** | 8 (0.70%) | 21 (0.93%) | 9 (0.82%) |

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

This nominally significant association between hyperchloremia and abnormalities in renal labs for patients taking celecoxib (or the active control) persisted if one examined only those subjects with more pronounced elevations in serum BUN, creatinine, and urine glucose/pH (data not shown).

The individual patient records were reviewed for those patients who had both hyperchloremia and one or more other lab abnormalities at the last available visit, and the results are shown in the last row above. There was no clear difference between treatment groups, there was a higher % of such patients in the celecoxib and active treatment groups, relative to placebo.

Among these patients, there were five in the celecoxib group whose last $Cl^-$ was >113mmol/l, 2 in the active control group, and none in the placebo. These patients are listed below. The peak $Cl^-$ at last visit for the celecoxib group was 116 mmol/l. If one assumes an average Anion Gap of 6-13 (avg. 8) and a serum $Na^+$ of 140, this $CL^-$ of 116 would correspond to a $HCO_3$ of 16 meq/l.

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

| Patient # | Days on Study Drug | Baseline/ Final PO4- (mmol/l and mg/dl) | Baseline/ Final Cl- (mmol/l) |
|---|---|---|---|
| **Placebo (none)** | | | |
| **Celecoxib** | | | |
| **022-0861** | 87 | 1.16/ 0.81 | 107/ 115 |
| **054-1137** | 12 | 0.84/ 0.74[b] | 109/ 115 |
| **020-0357** | 85 | 1.07/ 0.84 | 112/ 114[b] |
| **023-1358** | 43 | 0.97/ 0.94 | 109/ 116[c] |
| **Active Control** | | | |
| **023-1350** | 43 | 0.97/ 0.94 | 109/ 116 |
| **022-1072** | 81 | 1.13/ 0.84 | 110/ 116 |
| **023-0389** | 29 | 1.03/ 0.87 | 106/ 115 |

a. Data from examination of individual line-listings from SAS datasets provided by sponsor.
b. Note that $HCO_3$ or $PO_4$ was abnormally elevated at time of entry.
c. This patient also had new, trace proteinuria at last clinic visit.

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1b. Association between hyperchloremia and abnormalities in serum BUN/ Crt/ PO4 and/or urine Glucose/ protein/ pH. Long-term open-label trial.

In addition, almost 10% of the subjects in the long-term open-label trials had a similar association between hyperchloremia and other renal lab abnormalities.

Table 5.1.4.2.7 Hyperchloremia and other renal lab abnormalities in the long-term trial[a].

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| Abnormality | Celecoxib N=4499 |
|---|---|
| **Chloride >110 mmol/l** | *593 (13.2%)* |
| **BUN >6.7 mmol/l** | 1995 (44.3%) |
| **Crt >132 mmol/l** | 53 (1.2%) |
| **$PO_4$ <0.97 mmol/l** | 1361 (30.3%) |
| **Urine Glucose >trace** | 200 (4.4%) |
| **Urine Protein >trace** | 274 (6.1%) |
| **Urine pH >7.5** | 68 (1.5%) |
| **Any of the above Lab Abnormalities** | 2853 (63.4%) |
| **Both Hyperchloremia and one or more other lab abnormality** | 444 (9.9%) |
| **Both Hyperchloremia & one or more other lab abnormality at last lab visit** | 26 (0.6%) |

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

The individual patient records were reviewed for those patients who had both hyperchloremia and one or more other lab abnormalities at the last available visit, and the results are shown in the last row above.

Among these patients, there were four patients whose last $Cl^-$ was >113mmol/l, who had other abnormalities (2 hypo-phosphatemia, one proteinuria). These patients are listed below. The peak $Cl^-$ at last visit for the celecoxib group was 115 mmol/l. If one assumes an average Anion Gap of 6-13 (avg. 8) and a serum $Na^+$ of 140, this $CL^-$ of 116 would correspond to a $HCO_3$ of 17 meq/l. There were no patients found who had a steadily increasing chloride concentration measured over several lab values. There was also no apparent association (in this long-term dataset) between glycosuria and hyperchloremia.

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

| Patient # | Days on Study Drug | Baseline/ Final $PO4^-$ (mmol/l and mg/dl) | Baseline/ Final $Cl^-$ (mmol/l) |
|---|---|---|---|
| **012-0504[c]** | 366 | 1.0/ 1.13 | 112/ 114 |
| **022-1433** | 83 | 1.10/ 0.90 | 109/ 114 |
| **022-0861** | 87 | 1.16/ 0.81 | 107/ 115 |

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

Finally, there were two patients with notable abnormalities in renal labs in this set, which are summarized below. One had a persistently, severely, low serum $PO_4$ associated with hyperchloremia. The other patient developed significant proteinuria associated with decreased serum $PO_4$.

Table 5.1.4.2.9. Patients receiving celecoxib in the long-term, open-label trial with other notable renal lab abnormalities[a].

| Patient # | Days on Study Drug | Baseline/ Final $PO4^-$ (mmol/l and mg/dl) | Baseline/ Final $Cl^-$ (mmol/l) |
|---|---|---|---|
| **022-0622** | 92 | 0.55/ 0.42 | 109/ 113 |
| **013-0401[C]** | 452 | 1.58/ 0.94 | 107/ 106 |

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

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2a. Association of urinary abnormalities in the controlled North American trials.

The sponsor also searched for a clustering of the urinary abnormalities described in the controlled trials. The three urinary labs that were measured that might occur as a part of a proximal renal tubular injury are proteinuria, glycosuria, and changes in urinary pH. Of these, the pH is the most variable, and of the least use diagnostically. There was an increased incidence of glycosuria in the celecoxib group relative to placebo, but the incidence of proteinuria was similar in all treatment groups. As shown in the table below, there was no trend detected towards an increased association between these urinary abnormalities in the celecoxib group.

Table 5.1.4.2.10. Association between glycosuria and other urinary abnormalities in controlled trials[a].

| Abnormality | Placebo N=1136 | Celecoxib N=2256 | Active Control N=1099 |
|---|---|---|---|
| **Urine Glucose >1+** | 21 (1.8%) | 62 (2.7%) | 17 (1.5%) |
| **Urine Protein >trace** | 43 (3.8%) | 85 (3.8%) | 48 (4.4%) |
| **Urine pH >8.5** | 0 (0%) | 0 (0%) | 2 (0.2%) |
| **Any of the above Lab Abnormalities** | 43 (3.8%) | 85 (3.8%) | 50 (4.5%) |
| **Both Glycosuria and one or more other lab abnormality** | 4 (0.4%) | 3 (0.1%) | 6 (0.5%) |

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

3a. Hyperchloremia and serum $Ca^{2+}$/ $PO_4$ abnormalities in controlled NA OA/RA trials.

There was also an association between low serum $PO_4$ and elevated serum $Cl^-$ in the subjects who received celecoxib and the active control, with the active control group being nominally significant versus placebo. There was no link with alterations in change in serum $Ca^{2+}$, however.

Table 5.1.4.2.11. Association between $Ca^{2+}$, $P0_4^-$, and $Cl^-$ abnormalities in controlled trials[a].

| Abnormality | Placebo N=1136 | Celecoxib N=2256 | Active Control N=1099 |
|---|---|---|---|
| **$PO_4$ <0.97 mmol/l** | 195 (17.2%) | 470 (20.8%) | 351 (31.9%) |
| **Chloride >110 mmol/l** | 48 (4.2%) | 178 (7.9%) | 82 (7.5%) |
| **Calcium <1.7 mmol/l** | 0 (0%) | 0 (0%) | 0 (0%) |
| **Calcium >2.74 mmol/l** | 1 (<0.1%) | 2 (<0.1%) | 2 (0.2%) |
| **Any of the above Lab Abnormalities** | 227 (20%) | 597 (26.5%) | 399 (35.3%) |
| **Both low $PO_4$ and high $Cl^-$** | 16 (1.4%) | 51 (2.3%) | 34 (3.1%) |
| **Both low $PO_4$ and high $Cl^-$ at last clinic visit** | 8 (0.70%) | 14 (0.62%) | 8 (0.73%) |

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

The number of patients who had at least two of the labs abnormal on their last clinic visit were tabulated, and are shown in the last row above. There was no difference between treatment groups. As discussed above in section 1.2, the severity of the $PO_4$/ Cl abnormalities were, however, greater in the celecoxib and active control groups. While no placebo patient had a Cl >113 at last clinic visit (associated with abnormal $PO4^-$), there were 4 such patients in the celecoxib group, and 3 in the active control group. Their baseline and final lab values are summarized in table 5.1.4.1.6 above.

In the long-term, open-label database, 247 (5.5%) of the celecoxib patients developed both hypophosphatemia and hyperchloremia during the study. Of these, 13 (0.3%) had both abnormalities at the end of the study.

4a. Proteinuria and development of elevated BUN/ Creatinine

The association between the development of trace proteinuria or greater and abnormally elevated BUN/ Creatinine (Crt) were examined using two levels of BUN/ Crt. For the patients with less marked elevations there was a nominally significant association between the development of proteinuria and elevated BUN/Crt in the celecoxib and active control groups.

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

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

a. Data from analyses performed by sponsor, and not independently confirmed by FDA.
b. P values 0.07 vs. placebo, using unadjusted chi square.

Next the individual labs from patients who developed proteinuria plus Crt >132 and BUN >6.7 mmol/l were reviewed, to see if there was a temporal association between the lab abnormalities. The number of patients who had at least two of the labs abnormal on their last clinic visit were tabulated, and are shown in the last row of the table above. As can be seen, a higher number of celecoxib and active control subjects in the controlled trials ended the trial with abnormal elevations in two of the three lab values.

Another measure of severity is to look at how significant the proteinuria was. In the celecoxib patients, 2 with no proteinuria at trial entry ended the trial with at least 2+ proteinuria and abnormally elevated BUN, compared with no such patients in the placebo group, and 3 patient in the active control group.

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

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

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

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

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

4b. Association between hyperchloremia and bony/ muscular abnormalities. Long-term open-label trial.

Finally, the potential consequences of prolonged acidosis were examined by looking for an association between hyperchloremia and the development of bony fractures. These fractures occur in untreated metabolic acidosis as a consequence of loss of $HCO_3$ and $PO_4$ from the bone in an attempt to buffer the acidosis.

In the short-term controlled data, there was no significant increase in the frequency of this combination in the celecoxib or active control groups.

Table 5.1.4.2.14. Association between hyperchloremia and bony AEs in controlled trials[a].

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

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

In the long-term trial, there were 5 pathological fractures, and 32 patients who had one or more bony AE in addition to hyperchloremia.

Table 5.1.4.2.15. Association between hyperchloremia and bony AEs in long-term open-label trial[a].

| Abnormality | Celecoxib N=4499 |
|---|---|
| **Chloride >110 mmol/l** | 593 (13.2%) |
| **Fractures, Accidental** | 63 (1.4%) |
| **Fractures, Pathologic** | 5 (0.1%) |
| **Myalgias** | 113 (2.5%) |
| **Both Chloride and one AE** | 32 (0.7%) |

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

### 5.1.5 Vital Signs

Data on the incidence of abnormal heart rates were collected during both the controlled and the open-label trials. The sponsor summarized the data in two ways: 1) the incidence of 'extreme' changes in BP, heart rate or weight; and 2) mean changes in the same parameters. In addition, changes in blood pressure (i.e., hypotension, hypertension) and pulse rate (i.e., bradycardia, tachycardia, asystole) were included in both the AEs and the SAEs collected in all trials.

Incidence of Extreme Changes in BP, Heart Rate or Weight

In the controlled North American OA/RA trials, there was no clinically significant differences between placebo and celecoxib in the incidence of any of these parameters. The reader is referred to the Integrated Safety Summary, Text table 85 for details.

In the long-term, open-label trial, again, there was wide variability in patient responses, and no clinically relevant pattern to suggest a consistent effect of celecoxib on BP, heart rate, or weight.

Mean Changes in BP, Heart Rate or Weight

In the controlled North American trials, several small, nominally significant differences were found between celecoxib and placebo. These are summarized below. Overall, no clinically significant effects were detected. Importantly, no significant effect on BP was detected. In data not shown, a similar pattern was seen for the 100-200 mg celecoxib dose-group. Shaded boxes differed from placebo with nominal significance ($p<0.05$).

Table 5.1.5.1 Changes in mean vital signs in the 12-week, controlled North American Arthritis trials of celecoxib from NDA 20-998[a,b].

| Vital Sign Measured (Change from baseline) | Placebo | Celecoxib 400 mg BID | Active Controls |
|---|---|---|---|
| **Systolic BP** | -2.1±0.5 | **-0.5±0.5*** | **-0.3±0.6*** |
| **Diastolic BP** | -0.6±0.3 | -0.5±0.3 | -0.5±0.3 |
| **Pulse Rate** | 0.8±0.3 | **-0.4±0.3*** | 0.3±0.4 |
| **Male Weight (Baseline ≤85 kg)** | 1.43±0.9 | 0.41±0.2 | **0.97±0.2*** |
| **Male Weight (Baseline >85 kg)** | -0.5±0.3 | **1.37±0.4*** | **0.56±0.2*** |
| **Female Weight (Baseline ≤70 kg)** | 0.89±0.6 | 0.22±0.1 | 0.41±0.1 |
| **Female Weight (Baseline >70 kg)** | -0.23±0.1 | **0.12±0.1*** | **0.24±0.1*** |

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

In the long-term, open-label trials, vital signs were measured at each office visit (weeks 2, 6 and 12, then months 6, 9, 12, 15, and final). Overall, there was no discernable, consistent effect of celecoxib detected (see ISS, Table 30.4 for details).

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Adverse Events and Serious Adverse Events Related to Vital Signs

Changes in blood pressure (i.e., hypotension, hypertension) and pulse rate (i.e., bradycardia, tachycardia, asystole) were included in both the AEs and the SAEs collected in all trials.

*AEs*

See section 4.1.3 above for details of the incidence of rhythm disturbances as AEs in the celecoxib database.

*SAEs*

For the controlled North American arthritis trials, the following rhythm disturbances (WHO classification) as SAEs occurred in single patients in one of the dose groups (placebo, celecoxib or active control): arrhythmia; arrhythmia (atrial); fibrillation (atrial); heart block; palpitation; syncope; and tachycardia (both atrial and ventricular). Hypertension, or aggravated hypertension, occurred in three subjects in the celecoxib group, and in no placebo or active control patients.

In the open-label trial, the following rhythm disturbances (WHO classification) as SAEs occurred in single patients: hypotension; arrhythmia; AV block; cardiac arrest; extrasystoles; fibrillation (ventricular); and heart block. There were four episodes of atrial fibrillation, 2 episodes of supraventricular tachycardia, and 2 episodes of bradycardia.

**ECGs and Special Examinations**

No long-term data on the effect of celecoxib on the incidence of ECG abnormalities were collected. During the short-term phase I-II trials, only study 071 collected baseline and follow-up ECGs. No significant findings were reported by the sponsor in this study.

### 5.1.6 Discontinuations

The next table shows a summary of the disposition of subjects in the phase II-III trials of celecoxib, including the dropouts. Note that a smaller % of the placebo patients completed the trial, primarily due to drop-outs from therapeutic failure.

Table 5.1.6.1 Disposition of subjects randomized in the combined North American controlled OA/RA trials[a].

| Patient Disposition | Placebo N=1864 | Celecoxib 50-400 mg BID N=5704 | Active Control N=2098 |
|---|---|---|---|
| **Randomized** | 1864 | 5704 | 2098 |
| **Completed** | 970 (52%) | 3971 (69.6%) | 1480 (70.5%) |
| **Discontinued (Total)** | 894 (48.0%) | 1733 (30.3%) | 618 (9.5%) |
| **Therapeutic Failure** | 680 (36.5%) | 1119 (19.6%) | 316 (15.1%) |
| **Adverse Event** | 114 (6.1%) | 398 (7.0%) | 203 (9.7%) |
| **Patient noncompliance** | 58 (3.1%) | 135 (2.4%) | 76 (3.6%) |
| **Lost to Follow-Up** | 17 (0.9%) | 36 (0.6%) | 14 (0.7%) |

a. Data from Integrated Safety Summary, Appendix Table 5.8.

Table 5.1.6.2 Disposition of subjects randomized in the long-term, open-label combined OA/RA trial[a].

| Patient Disposition | Celecoxib |
|---|---|
| **Randomized** | 4499 |
| **Completed** | 3317 (73.7%) |
| **Discontinued (Total)** | 1182 (26.3%) |
| **Therapeutic Failure** | 639 (14.2%) |
| **Adverse Event** | 296 (6.6%) |
| **Patient noncompliance** | 165 (3.7%) |
| **Lost to Follow-Up** | 46 (1.0%) |

a. Data from Integrated Safety Summary, Appendix Table 5.9.

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**Discontinuations associated with Adverse Events (AEs)**

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

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

| Body System/ AE | Placebo N=1864 | Celecoxib 50-400 mg BID N=5704 | Active Control N=2098 |
|---|---|---|---|
| **Total # with AEs leading to discontinuation** | 114 (6.1%) | 298 (7.0%) | 203 (9.7%) |
| **Hypertension[b]** | 0 (0%) | 6 (0.1%) | 1 (<0.1%) |
| **Hypotension, includes postural** | 0 (0%) | 1 (<0.1%) | 2 (<0.1%) |
| **Edema, peripheral** | 1 (<0.1%) | 4 (<0.1%) | 1 (<0.1%) |
| **Edema, facial** | 3 (0.2%) | 7 (0.1%) | 2 (0.1%) |
| **Edema, Generalized** | 0 (0%) | 1 (<0.1%) | 2 (0.1%) |
| **Arrhythmia[c]** | **1 (<0.1%)** | **9 (0.16%)** | **3 (0.14%)** |
| **Arteritis/ Vasculitis** | 0 (0%) | 1 (<0.1%) | 0 (0%) |
| **Angina[d]** | 2 (0.1%) | 2 (<0.1%) | 1 (<0.1%) |
| **Myocardial infarction** | 2 (0.1%) | 6 (0.1%) | 2 (0.1%) |

a. Data from Integrated Safety Summary, Appendix table 6.4..
b. Includes hypertension, aggravated hypertension.
c. Includes 'arrhythmia', atrial arrhythmia, atrial fibrillation, palpitation, tachycardia, and supraventricular tachycardia.
d. Includes angina pectoris, aggravated angina pectoris and unstable angina.

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

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

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

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

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

a. Data from Integrated Safety Summary, Appendix table 9.6.
b. Includes hypertension, aggravated hypertension.
c. Includes coronary thrombosis.
d. Includes 'angina pectoris.'

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

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

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

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

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

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

a. Data from sponsor at reviewer's request.

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

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

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

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

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## 5.2 Integrated Summary of Renal and Cardiac Safety

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

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

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

### 5.2.1 Limitation of NDA Dataset for Detecting Renal and Cardiovascular AEs

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

**Patient Exposure**

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

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

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

**Data Collection**

There is obviously a trade-off between the desire on the part of the FDA for complete safety information and the practicalities of performing large clinical trials. For the development of celecoxib, the sponsor did not collect serum bicarbonate data, normally a routine part of serum electrolytes. One possible explanation was the use of central lab facilities, which precludes the accurate measurement of $HCO_3$ unless labor-intensive steps are taken. As is clear from the above analyses, this omission, in association with the significantly increased incidence of hyperchloremia, forces the use of other, less clear-cut, markers for acid-base balance. Ultimately, this decision means that the data needed to resolve questions related to the effect of celecoxib on acid-base balance will simply not be available.

### 5.2.2 Occurrence of Significant Cardiovascular AEs and SAEs

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

### 5.2.2a Cardiovascular Mortality

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

***Mortality in deaths per patients exposed***

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

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

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

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

***Mortality in deaths per patient-years of exposure***

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

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

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

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

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

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*Cardiovascular mortality derived from Kaplan-Meier Plot*

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

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

a. Data from sponsor-derived plots.

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

*Mortality in deaths per patients exposed*

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

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

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

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

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

*Mortality in deaths per patient-years of exposure*

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

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

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

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

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

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

*Cardiovascular mortality derived from Kaplan-Meier Plot*

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

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

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

a. Data from sponsor-derived plots.

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

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

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

a. Data from Integrated Safety Summary, including Text Tables 65-68.
b. Data shown for deaths that occurred prior to cut-off date 11.21.97.
c. Mortality (for both total and cardiovascular deaths) in deaths/pt-yrs (x100).
d. Data from ISS, Appendix table 4.3.

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

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

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

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

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

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

**Conclusion regarding cardiovascular mortality**

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

1) the increased relative rate of cardiovascular death in the celecoxib and active control groups during the controlled trials (0% for placebo, 0.02% for celecoxib, 0.12% for active control, see table 5.1.1.2.5),

2) the apparent relationship between dose of celecoxib and rate of cardiovascular death in the long-term, open-label trial (table 5.1.1.2.7), and

3) the preponderance of deaths due to cardiovascular disease in the open-label trial (tables 5.1.1.1.1 through 5.1.1.1.4).

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

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

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

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

The available data are inadequate either to exclude or confirm a link between celecoxib administration and cardiovascular death.

### 5.2.2b Blood Pressure Effects

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

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

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

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

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

**3.** There was a higher incidence of 'hypertension' as an AE in the celecoxib and active control groups, relative to placebo (table 5.1.3.1).

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

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

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

c. Includes both undifferentiated hypertension and aggravated hypertension.

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

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

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

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| Treatment Group/ Patient # | Preferred Term for AE |
|---|---|
| **Placebo** | |
| **None** | |
| **Celecoxib 50-400 mg** | |
| **020-0123** | Hypertension |
| **020-0294** | Hypertension |
| **020-1147** | Hypertension, Aggravated |
| **054-0153** | Hypertension |
| **054-1396** | Hypertension, Aggravated |
| **071-2008** | Hypertension, Aggravated |
| **Active Control** | |
| **071-1737** | Hypertension |

a. Data from sponsor at reviewer's request.

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

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

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

**Conclusions regarding blood pressure**

The available data are sufficient to conclude that there is an association between celecoxib and active control administration and the worsening of blood pressure in some patients. This worsening is primarily seen within 12 weeks of starting the treatment, but is of sufficient severity to lead to subject withdrawal from the study drug in both the short-term controlled and in the long-term studies.

### 5.2.2c Edema Formation

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

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

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

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

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

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

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

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

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

a. Data from sponsor at reviewer's request.

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

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

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

a. Data from sponsor at reviewer's request submitted 11.3.98 .
b. Dose is last recorded does taken by the patient at time of AE.

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

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

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

a. Data from corrected tables from the ISS. table 3.1.3.6. dated 9.16.98 including only 100 and 200 mg dose groups.
b. Data from sponsor. only for those patients with both weight and edema AE data. Includes 50 to 400 mg doses.

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

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

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

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

b. * represent nominal significance versus placebo.

**Conclusion regarding edema**

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

### 5.2.2d Rhythm disturbances

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

From Table 5.1.5.1 Mean changes in pulse rate in the controlled North American arthritis trials[a,b].

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

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

b. * indicates nominally significant difference with placebo.

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

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

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

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

d. Includes undifferentiated arrhythmia, atrial and ventricular arrhythmia.

e. Includes undifferentiated and supraventricular tachycardia.

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

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

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

a. Data from NDA Integrated Safety Summary, Appendix Table 22.1, and electronic datasets.
b. Includes the following terms: arrhythmia; atrial arrhythmia; atrial fibrillation; heart block; palpitation; & supraventricular tachycardia.

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

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

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

a. Data from NDA Integrated Safety Summary, Table 22.2, and electronic datasets. Numbers shown as individual subjects. Note that in some cases, a subject may have had more than one serious adverse event in the same category, which is not captured here.
b. Includes coronary thrombosis and myocardial infarction.

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

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

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

a. Data from Integrated Safety Summary, Appendix table 6.4..
c. Includes 'arrhythmia', atrial arrhythmia, atrial fibrillation, palpitation, tachycardia, and supraventricular tachycardia.

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

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

**Conclusion regarding arrhythmias**

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

### 5.2.2e Heart failure

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

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

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

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

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

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

**Conclusion regarding heart failure**

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

### 5.2.2f Myocardial infarction and Angina Pectoris

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

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

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

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

c. Includes both undifferentiated hypertension and aggravated hypertension.

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

g. Includes 'Thrombosis, coronary'.

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

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

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

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

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

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

**Conclusion regarding myocardial ischemic adverse events**

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

### 5.2.3 Renal Adverse Events

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

### 5.2.3a Clinical Renal Adverse Events

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

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

1. Patient 047-0030 was a 70-year-old female with a prior history of labile vascular hypertension, and urinary system disorders including urethral stenosis, urgency, and bladder spasms. Concomitant medications were: captopril, chlorpheniramine, docusate sodium, aspirin, estrogen, etidronate, fluconazole, dexamethasone, oxybutynin, pravastatin, quinine sulfate, and verapamil. Three weeks after starting celecoxib 400 mg BID, she experienced leg cramps for which she took quinine and subsequently experienced headache and pruritus. One week later, she repeated a single dose of quinine and again experienced headache and pruritus, but also nausea, vomiting, diarrhea, chills, and confusion. Four days later she was hospitalized with a fever and a creatinine level of (b)(4) She was diagnosed with hemolytic uremic syndrome presumed due to quinine sulfate. Treatment included plasmapheresis, hemodialysis, and platelet transfusion.

2. Patient 024-1490002 was a 65- year-old male with a medical history of hypertension, depression, nocturia and RA. Concurrent medications included gold sodium thiomalate, terazosin, fosinopril, metoprolol, prednisone, and combination perphenazine and amitriptyline. The patient took celecoxib 100 mg BID for 12 weeks in a double-blind clinical RA trial. After successfully completing the trial, he was admitted to the long-term open-label trial. He was instructed to take celecoxib 200 mg BID, but for unknown reasons, he took only 100 mg BID. The patient returned at week 2 and no abnormalities were noted. Four days after he was seen for his "Week 6" visit, his urine output decreased and he felt ill. This was approximately one week following an endoscopic procedure associated with anesthesia. (Laboratory results from the Week 6 Visit revealed his serum creatinine to be (b)(4) and his BUN to be (b)(4) significantly higher than his Baseline values, which were (b)(4) respectively). Five days later, study medication was stopped when he was hospitalized with a serum creatinine level of (b)(4) and a BUN (b)(4) During his hospitalization, he required hemodialysis on two occasions. Ultrasound examination showed bilateral hydronephrosis. He was scheduled for cystoscopy and retrograde ureteroscopy and possible stent placement when he developed significant large volume diuresis with normalization of his renal function. He recovered and was discharged from the hospital five days later. One week later, his serum creatinine value was (b)(4) mg/dL and his BUN was (b)(4)

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

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

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

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

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

3. There were several other patients who experienced renal SAEs requiring discontinuation from the controlled and open-label trials. These are summarized below. Note in the open-label withdrawals that for many of the patients the adverse event was ongoing at time of last information. Using the patients listed below, the relative rates of withdrawal for 'renal adverse events' were 0.21%, 0.27%, and 0.24% for the placebo, celecoxib and active control groups, respectively.

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

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

a. Data from sponsor at reviewer's request.

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

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

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

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

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

**Conclusion regarding clinical renal adverse events**

The NDA does not reveal a strong signal pointing towards substantial clinically serious renal disease (i.e., large number of patients with acute renal failure requiring dialysis, nephrotic syndrome) associated with celecoxib administration. There are individuals with substantial clinical AEs who received. In particular, the increased % of subjects withdrawn due to worsened hypertension and edema in both the short- and long-term trials suggest, in combination with the observed effects of celecoxib on these parameters otherwise (see below), that celecoxib is not placebo with regard to its potential clinically-relevant renal effects. A larger database would be necessary to determine the occurrence rates for rarer, more serious renal AEs such as papillary necrosis, nephrotic syndrome or interstitial nephritis.

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### 5.2.3b Changes in Renal Laboratories

**Changes in BUN**

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

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

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

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

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

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

| Maximal Change in Lab Value | Placebo | Celecoxib 400 mg | Active Controls |
|---|---|---|---|
| **BUN (mmol/l)** | | | |
| [redacted] | 5/420 from Normal | 17/409 from Normal | 21/423 from Normal |
| **Extreme high** | [redacted] | | |

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

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

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

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

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

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

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

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

a. Data from data submitted to FDA 10.9.98 from sponsor, and not independently confirmed by FDA reviewer.
b. 20 mg/dl.
c. 40 mg/dl.

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

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

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

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

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

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

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

a. Data from data submitted to FDA 10.9.98 from sponsor.
b. 20 mg/dl.
c. 40 mg/dl.
d. 1.5 mg/dl.
e. 1.8 mg/dl
f. 3.0 mg/dl.

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

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

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

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

Conclusions regarding BUN

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

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**Changes in Creatinine**

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

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

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

a. Data from data submitted to FDA 10.9.98 from sponsor, and not independently confirmed by FDA reviewer.
d. 1.5 mg/dl.
e. 1.8 mg/dl

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

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

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

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

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a. Data from sponsor at reviewer's request.

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

**Conclusions regarding elevated BUN and Creatinine**

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

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### 5.2.3c Proteinuria and other Urinary Abnormalities

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

b. P values 0.07 vs. placebo, using unadjusted chi square.

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

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

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

| Patient # | Days on Celecoxib | Baseline/ Final Crt (mmol/l | Baseline/ Final BUN (mmol/l) |
|---|---|---|---|
| 014-0002 | 484 | 168/ 239 (b)(4) | 14.3/ 26.1 (b)(4) |
| 013-70004 | 183 | 53/ 168 ( | 7.9/ 15.4[b] |
| 14-90002 | 122 | 124/ 760 | 10.7/ 21.8 |

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

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

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

| Celecoxib Dose[b]/ Patient # | Final Dose | Adverse Event |
|---|---|---|
| **Celecoxib 200 mg** | | |
| 020-1071 | 200 | Proteinuria, Albuminuria |

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

**Conclusion regarding urinary abnormalities**

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

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

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

### 5.2.3d Changes in Serum Electrolytes

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

**Potassium, Sodium, Calcium**

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

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

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

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

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

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

| Maximal Change in Lab Value | Celecoxib 400 mg | Placebo | Active Controls |
|---|---|---|---|
| **Potassium (mmol/l)** | | | |
| **High** (b)(4) | 20/399 from Normal (5.0%) | 8/416 from Normal (1.9%) | 20/419 from Normal (4.8%) |
| | (b)(4) | | |

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

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

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

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

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

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

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

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

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

1. Patient #024-US0033-0330007 was a 72-year-old female with history of hypertension, venous insufficiency, hypercholesterolemia, and hypothyroidism. Concurrent medications included hydrochlorothiazide, triamterene, verapamil, and calcium. This patient took celecoxib 300 mg BID for 14 days before discontinuing because of treatment failure. Two days after stopping celecoxib, she was hospitalized with a plasma sodium level of (b)(4) She received IV fluid and her plasma sodium returned to normal. Her hospital diagnosis indicated metabolic encephalopathy secondary to hyponatremia most likely due to diuretic therapy.

2. Patient 024-US0013-0130009 was a 78-year-old female with a history of hypertension, urinary complaints, and elevated liver function tests. Concurrent medications included doxazosin, Moduretic and indapamide. The patient initiated treatment with celecoxib 200 mg BID and experienced sinusitis eight-and-one-half months later. She was treated with antibiotics but three days later she lost consciousness and was incontinent of urine. Following this syncopal episode, she vomited. She was taken to the hospital, where her serum potassium and sodium were found to be (b)(4) respectively. She was rehydrated with intravenous solution, treated with potassium, and indapamide was discontinued. Amoxicillin was continued to treat the sinusitis. Her hyponatremia is also presumed to be secondary to diuretic therapy

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

**Conclusion regarding sodium, potassiuim, and calcium lab abnormalities**

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

**Chloride and Phosphate/ Disorders of Acid-Base Status**

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

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

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

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

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

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

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

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

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

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

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**3.** Patients in the celecoxib group were significantly more likely to have serum chloride >110 mmol/l and $PO_4$ <0.97 mmol/l during the 12 week controlled trials, when compared with placebo.

From Table 5.1.4.2.3 Incidence of abnormal Cl and $PO_4$ the North American 12-week Arthritis trials.

| AE/ Lab Value | Placebo N=1136 | Celecoxib 100 mg N=1131 | Celecoxib 200 mg N=1125 | Celecoxib 400 mg N=434 | Active Control N=1099 |
|---|---|---|---|---|---|
| **Chloride >110 mmol/l** | **48 (4.2%)** | **90 (8.0%)** | **88 (7.8%)** | **37 (8.5%)** | **82 (7.5%)** |
| **Chloride >120 mmol/l** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **$PO_4$ <0.97 mmol/l[f]** | 195 (17.2%) | 233 (20.6%) | 237 (21.1%) | 83 (19.1%) | 351 (31.9%) |

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

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

Table 5.1.4.2.11. Association between $Ca^{2+}$, $PO_4^-$, and $Cl^-$ abnormalities in controlled trials[a].

| Abnormality | Placebo N=1136 | Celecoxib N=2256 | Active Control N=1099 |
|---|---|---|---|
| **$PO_4$ <0.97 mmol/l** | 195 (17.2%) | **470 (20.8%)** | **351 (31.9%)** |
| **Chloride >110 mmol/l** | 48 (4.2%) | **178 (7.9%)** | **82 (7.5%)** |
| **Both low $PO_4$ and high $Cl^-$** | 16 (1.4%) | 51 (2.3%) | **34 (3.1%)** |
| **Both low $PO_4$ and high $Cl^-$ at last clinic visit** | 8 (0.70%) | 14 (0.62%) | 8 (0.73%) |

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

**4.** Patients in the celecoxib and active control groups were also more likely to have chlorides >113 at the time of their last visit in addition to decreased $PO_4$..

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

| Patient # | Days on Study Drug | Baseline/ Final $PO4^-$ (mmol/l and mg/dl) | Baseline/ Final $Cl^-$ (mmol/l) |
|---|---|---|---|
| **Placebo (n=1136)** | | | |
| **None** | | | |
| **Celecoxib (n=2256)** | | | |
| **022-0861** | 87 | 1.16/ 0.81 | 107/ 115 |
| **054-1137** | 12 | 0.84/ 0.74[b] | 109/ 115 |
| **020-0357** | 85 | 1.07/ 0.84 | 112/ 114[b] |
| **023-1358** | 43 | 0.97/ 0.94 | 109/ 116[c] |
| **Active Control (n=1099)** | | | |
| **023-1350** | 43 | 0.97/ 0.94 | 109/ 116 |
| **022-1072** | 81 | 1.13/ 0.84 | 110/ 116 |
| **023-0389** | 29 | 1.03/ 0.87 | 106/ 115 |

a. Data from examination of individual line-listings from SAS datasets provided by sponsor.
b. Note that $HCO_3$ or $PO_4$ was abnormally elevated at time of entry.
c. This patient also had new, trace proteinuria at last clinic visit.

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

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

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

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

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

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

| Patient # | Days on Study Drug | Baseline/ Final PO4- (mmol/l and mg/dl) | Baseline/ Final Cl- (mmol/l) |
|---|---|---|---|
| 012-0504[c] | 366 | 1.0/ 1.13 | 112/ 114 |
| 022-1433 | 83 | 1.10/ 0.90 (low) | 109/ 114 |
| 022-0861 | 87 | 1.16/ 0.81 (low) | 107/ 115 |

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

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

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

| Patient # | Days on Study Drug | Baseline/ Final PO4- (mmol/l and mg/dl) | Baseline/ Final Cl- (mmol/l) |
|---|---|---|---|
| 022-0622 | 92 | 0.55/ 0.42 | 109/ 113 |
| 013-0401[C] | 452 | 1.58/ 0.94 | 107/ 106 |

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

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

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

From Table 5.1.3.1 AEs related to $PO_4$ and $Cl^-$ in the N.A. Arthritis trials of celecoxib from NDA 20-998[a].

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

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

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

**10.** An analysis of those individuals who received bicarbonate or citrate therapy revealed no increase in their use among the celecoxib group. Where identified, patients received these products for GI reasons primarily, and noone was identified as receiving them for systemic acidosis. The use of acetazolamide was also balanced between the treatment groups.

**Conclusion regarding chloride and phosphate lab abnormalities**

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

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

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

**5.3 Recommendations of Renal/ Cardiac Consultant**

**General Summary**

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

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

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

**Cardiac Safety**

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

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

**Renal Safety**

Three trials were performed on specific populations (elderly patients, patients with mild-to-moderate renal insufficiency, patients with volume contraction) to examine their renal responses to celecoxib. These trials examined the short-term effects of celecoxib on the excretion of prostaglandins, as well as a variety of other renal parameters. Given the small numbers of patients, the short trial durations, and the broad patient-patient variability, the broadest conclusion is that, under the conditions of those trials, both celecoxib and the comparator NSAIDs had significant inhibitory effects on the excretion of the urinary prostaglandins when compared with placebo. In particular, celecoxib and the comparator NSAIDs inhibit prostaglandin $PGE_2$ and 6-keto-$PGF_1$-alpha excretion by the kidney to more or less the same extent over the duration of the individual trials.

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**Renal Safety (cont)**

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

1) The first was that all three treatment groups would show similar patterns of renal effects, including lab abnormalities and clinical adverse events. In this case, a reasonable conclusion would be that the database was underpowered, as it was not able to differentiate between placebo and the active control NSAIDs, which know renal toxicity. This was not the case in this database, and there was clear separation of placecbo and NSAIDs, especially with regard to lab abnormalities.

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

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

There is sufficient evidence to conclude that both celecoxib and the active controls demonstrated significant renal effects in the NDA, as reflected in the pattern of lab abnormalities associated with their administration. This pattern includes an association between celecoxib and 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 celecoxib and the other NSAIDs have similar renal effects.

There were no cases of acute renal failure in either the celecoxib or the active controls in the controlled trials. Given the known nephrotoxicity of NSAIDs, the absence of adverse clinical renal events in the controlled trials can be attributed to the low event rate, and does not mean that they do not occur. While there were no clear cases of celecoxib-induced renal failure in the controlled OA/RA trials, there were several individuals on celecoxib in the long-term, open-label trial who were withdrawn because of renal adverse events, including acute renal failure (as well as edema and worsening hypertension). While a direct link between events in open-label experience and celecoxib cannot absolutely be made with the available data, they are consistent with the patterns of clinical renal disease seen with other NSAIDs.

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

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 and the comparator NSAIDs are clearly distinguished from placebo. It remains to be determined is whether renal injury will occur following celecoxib at the same rate that is seen with other NSAIDs.

### 5.3.1 References


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### 6.1 Appendix One: Deaths in the Celecoxib NDA Database

#### 6.1.1 Deaths in patients who enrolled in a controlled arthritis trial

**1. Patient No. BE0002-0010** (Carcinoma–Gallbladder to Liver) was a 70 year old male with a past history including cardiomyopathy, pulmonary hypertension, COPD, hyperthyroidism, cholelithiasis, hypercholesterolemia, hypergammaglobulinemia, and an enlarged liver was admitted to study and randomized to the celecoxib 200 mg BID treatment group. Patient began taking study medication on 5 February 1997. Seventy nine days after the start of dosing on 26 April 1997 the patient stopped taking study medication because of nausea. On 11 May 1997 he saw his general practitioner because of sudden nausea, vomiting and intermittent diffuse abdominal pain. The patient was hospitalized on 12 May 1997 for further investigation. His bilirubin and liver enzymes were elevated. He was found to have carcinoma of the gallbladder with metastases to the liver. He also had mild macrocytic anemia with no evidence of bleeding. Laboratory work included: 21 April 1997 (b)(4) [redacted] during hospitalization ECHO and CT (b)(4) [redacted] (b)(4) [redacted] The patient died on 21 May 1997 due to the carcinoma. No autopsy was performed.

**2. Patient No. US0117-46761235** (Cerebrovascular Disorder) was a 68 year old male with a history of tonsillectomy, bilateral otitis externa, herpes zoster, post-herpatic neuralgia, arteriosclerotic cardiovascular disease, bilateral claudication, hypertension, removal of abdominal aortic aneurism, appendectomy, hemorrhoidectomy, right great toe fracture, mild scoliosis, hypercholesterolemia, and OA. The patient was enrolled into the study on 14 July 1997 and randomized to receive naproxen 500 mg BID. After 63 days of treatment, the patient could not get out of bed. He had right-sided weakness and felt he would fall if he tried to stand. He felt "very funny" and had blurred vision and slurred speech. He was taken to the emergency room where his blood pressure was elevated at (b)(4) [redacted] Central nervous system examination revealed slurred speech, blurred vision, mild vertical nystagmus, and abnormal right upper extremity finger-to-nose. Other physical examination was normal. Initial lab data was unremarkable. A CT scan of the head did not reveal any acute hemorrhage. Chest x-ray revealed mild cardiomegaly. Brain stem evoked potential was suggestive of acute brain stem infarct. The patient was admitted to the hospital and intravenous enalapril maleate was initiated. He was also treated with metoprolol tartrate and sublingual nifedipine. His speech and coordination improved somewhat the following day, but later that day he developed focal seizures and became unresponsive. He was treated with intravenous diazepam and phenytoin but remained unresponsive. His blood pressure was (b)(4) [redacted] it was felt that he had probably had an extension of his initial brain stem cerebrovascular accident. He was intubated and was started on intravenous antibiotics. Blood cultures were negative. The patient died four days later. No autopsy was performed. Concomitant medications included quinapril, metoprolol succinate SR, doxepin, and atrovastatin.

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

**4. Patient No. US0333-46521451** (Arteriosclerosis) was a 53 year old female with a history of hypertension, hysterectomy, allergy to codeine, and osteoarthritis. The patient was enrolled into the study on 25 August 1997 and randomized to receive diclofenac 75 mg BID. On September 9, 1997, the patient was found dead at home by her daughter. Since the patient's family never returned the study medication containers, compliance or length of study medication cannot be determined. Her daughter stated the patient had " probably been dead for about one hour" when she was found. She also stated that the coroner's report listed the cause of death as "hypertensive cardiovascular disease." Concomitant medications included fluoxetine hydrochloride, buspirone hydrochloride, and losartan.

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

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

**1. Patient No. US0033-0768** (Myocardial Infarction) was an 80-year-old female with a history of OA, hypertension, borderline diet-controlled diabetes, hysterectomy, appendectomy, cholecystectomy, lumbar laminectomy, anterior cervical decompression and fusion, cataract surgery and rectal surgery for fistulas. The patient was enrolled into the study on 18 October 1996 and randomized to receive celecoxib 200 mg BID. After five days on treatment, the patient experienced severe chest pain lasting three hours which was associated with vomiting, diaphoresis and shortness of breath. She was hospitalized for an inferior wall myocardial infarction. It was noted that the patient had experienced intermittent chest pain for three days prior to hospital admission and had complained of anginal symptoms which occurred both with activity and at rest for six months prior to enrollment into the study. Treatment included aspirin, tissue plasminogen activator or a novel plasminogen activator under investigation. Additional treatment included morphine, intravenous heparin, intravenous nitroglycerin, ticlopidine and metoprolol. An ECG demonstrated ST fullness in the inferior leads with T-wave inversion and ST elevation with right-side ECG in V4-V6. A chest x-ray showed cardiomegaly and an atherosclerotic aorta with no other acute abnormalities. Emergency left heart catheterization was performed showing (b)(4) occlusion of the mid-right coronary artery. Percutaneous transluminal coronary angioplasty was performed with suboptimum blood flow; therefore, a coronary stent was deployed which was successful. Concomitant medication included triamterene/hydrochlorothiazide, diphenoxylate/atropine and alprazolam. Study medication was discontinued and the patient was terminated early from the study. The patient was discharged from the hospital and reported feeling well. The patient was unable to schedule the Early Termination visit. Forty-five days following onset of the event, the patient expired in her sleep. No autopsy was performed. The death certificate listed immediate cause of death probable myocardial infarction due to coronary artery disease and congestive heart failure.

**2. Patient No. US0052-0683** (Pulmonary Carcinoma) was a 62-year-old female with a history of tobacco use, no taste or smell, hysterectomy, pneumonia, hypertension, arthroscopy, fibromyalgia, degenerative disc disease and OA. The patient was enrolled into the study on 19 September 1996 and randomized to receive celecoxib 100 mg BID. Eight days after treatment began, the patient was referred to a pulmonologist for increased dyspnea. Chest x-ray revealed a right upper lung nodular density. On Study Day 12, a CT scan of the patient's chest showed a (b)(4) spiculated right upper lobe mass, consistent with a carcinoma. Bronchoscopy was performed thirteen days later and bronchoalveolar lavage cytology report showed atypical cells that were non-diagnostic. Study medication was discontinued at this time and the patient was withdrawn from the study. Thirty-four days later the patient was admitted for a right upper lobe lung mass. A thoracotomy with right upper and middle lobectomy was performed. No evidence of metastatic disease was found. The patient developed post-operative atelectasis with possible pneumonia three days later which advanced to adult respiratory distress syndrome (origin unknown) ending in death sixteen days after onset. No autopsy was performed. Other concomitant medications included nifedipine, fluoxetine, estradiol, cephalexin and minocycline.

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

collection in the right upper quadrant. CT scan showed a large periduodenal hematoma. The patient's white blood cell count and amylase were elevated and some degree of pancreatitis was also suspected. A central line was placed, the patient was started on total parenteral nutrition and anticoagulant therapy was discontinued. The patient then developed some hallucinations and erratic behavior and bizarre complaints, and eight days after surgery, apparently suffered a cardiopulmonary arrest. The patient was resuscitated and was transferred to intensive care. His ECG at that time showed tachycardia with left bundle branch block. Shortly after transfer to the unit, he developed an idioventricular rhythm and was pulseless. Resuscitation attempts were unsuccessful and the patient was pronounced dead. It was the opinion of the cardiologist who attended the event that he had either suffered a massive myocardial infarction or massive pulmonary embolus. An autopsy was not done. No other concomitant medications were being taken. Study medication was interrupted during hospitalization.

**4. Patient No. US0001-0053** (Death) was a 66 year old female with a history of cataracts, appendectomy, hemorrhoidectomy, postmenopause, fibrocystic breast disease, bilateral mastectomy, bilateral breast implant, squamous cell carcinoma, iron deficient anemia, multiple drug allergies, and RA. The patient had previously participated in the N49-96-02-022 clinical trial during which she had received placebo. After successfully completing this study, she was entered into the long-term safety study and began taking celecoxib 200 mg BID on 25 February 1997. Dosage was increased to 300 mg BID 42 days later on 8 April 1997. Nine days after that on 17 April 1997, the patient had a basal cell carcinoma removed from the right side of her nose. One hundred and thirty three days later (on 28 August 1997), dosage was increased to 400 mg BID. Approximately 12 days later, on or about 9 September 1997, the patient died of "natural causes." Concomitant medications included prednisone, methotrexate sodium, folic acid, and ferrous sulfate.

**5. Patient No. US0001-0076** (Heart Block, Hypoglycemia,Hyperglycemia) was a 74 year old male with a history of seasonal allergies, pericarditis,prostate surgery for benign prostatic hypertrophy, bilateral ankle fusion, psoriasis, snoring, hypertension, chronic obstructive pulmonary disease, and rheumatoid arthritis. The patient previously participated in celecoxibclinical trial #N49-96-02-022, during which the patient had received either placebo, celecoxib 100 mg BID, 200 mg BID, 400mg BID or naproxen 500 mg BID. After being withdrawn early due to treatment failure, he was entered into the long-term safety study, N49-96-02-024, and began taking SC-58635200 mg BID on April 23, 1997. Dosage was adjusted to 300 mg BID 5 days later, on April 28, 1997 and to 400 mg BID 4 days later, on May 2, 1997. Three hundred and twenty-seven days later, on March 25, 1998, the patient was wheeled into the doctor's office and was cyanotic and lethargic. The patient was incubated and taken to the emergency room where he was pronounced dead. The patient was diagnosed as being in total heart block, hypoglycemic (blood sugar (b)(4) and hyperkalemic (b)(4) Amphetamines and antidepressants were detected in the patient's urine. The patient had gone to see his primary care physician one day prior to this event, on March 24, 1998, and the physician said the patient was "OK". Concomitant medications included prednisone, pencillamine, trinallin and amlodipine. The date of last dose is unknown at this time.

**6. Patient No. US0023-0020** (Myocardial Infarction, Cardiac Failure) was a 76 year old male with a history of appendectomy, testicle cyst (removed), malaria, diabetes, sinusitis, insomnia, fractures of foot, shoulder and nose, hyperlipidemia, hypertension and RA. The patient had previously participated in the N49-96-02-023 clinical trial during which he had received naproxen 500 mg BID. After terminating early from this study due to treatment failure, the patient entered into the long term safety study and began taking celecoxib200 mg BID on 1 April 1997. After 23 days of treatment, on 24 April 1997, the patient was hospitalized for a previously scheduled total hip replacement. After 39 days of treatment, on 15 May 1997, the patient was hospitalized for a right deep venous thrombosis. Seven days after discharge, on 26 May 1997, the patient was seen in the emergency room for constant anterior chest pain, which had began approximately two days earlier and was not associated with radiation, diaphoresis,or dyspnea. The patient was then hospitalized the following day, on 27 May 1997, with a myocardial infarction of the anterior wall. Treatment included intravenous nitroglycerin and heparin sodium, oxygen, and monitoring and evaluation of cardiac status. Lab work revealed glucose of (b)(4) (b)(4) Ventilation-perfusion lung scan performed due to an episode of shortness of breath showed a low probability of a pulmonary embolus. Portable chest x-ray showed no acute cardiopulmonary disease. Echocardiogram showed normal left ventricular contractility, ejection fraction of approximately (b)(4) normal intracardiac chambers, and normal valvular function. Cardiac catheterization performed six days later, on 2 June 1997, showed coronary artery disease with (b)(4) left main proximal stenosis, 100% left circumflex distal stenosis, left anterior descending with someplaquing in the midportion but no focal stenosis more than (b)(4) mid right coronary artery stenosis, and left ventricular ejection fraction of (b)(4) The patient was then transferred to another hospital that same day, (continued)

where he underwent a percutaneous transluminal coronary angioplasty with stenting of the right coronary artery. Nine days after transfer and approximately one week after discharge, on 11 June 1997, the patient developed a sudden onset of chest pain which was not relieved by three sublingual nitroglycerin. The patient was taken to the emergency room and was intubated and cardioverted after experiencing sustained ventricular tachycardia, ventricular fibrillation, and cardiac arrest. The patient was then admitted for an acute inferior wall myocardial infarction probably due to acute closure of the right coronary stent placed two weeks prior to admission, complicated by cardiogenic shock, hypotension with systolic blood pressure (b)(4) and bradycardia with heart rate in the 30's. Electrocardiogram confirmed an acute inferior infarct showing acute ST segment elevation, severe bradycardia, and third degree heart block. Despite being on warfarin sodium, his protime was only (b)(4) Treatment included a temporary pacemaker as well as intravenous fluids, oxygen, morphine sulfate, Levophed, thrombolytic therapy, heparin sodium, and dopamine hydrochloride. The patient expired the following day, on 12 June 1997, due to cardiogenic shock and acute myocardial infarction after an unsuccessful resuscitation attempt for pulseless ventricular fibrillation. Other concomitant medications included Centrum, multivitamins, metformin hydrochloride and nisoldipine.

**7. Patient No. US0024-0024** (Coronary Artery Disorder) was a 71 year old male with a history of hypertension, myocardial infraction, peripheral bilateral edema due to cardiovascular disease, removal of ganglion cyst on left elbow, dentures, not-fasting hyperglycemia, hypercholesterolmia, hypertriglycaridemia, hypocalcemia, macular degeneration of right eye, right inguinal hernia repair, urinary tract infection, and rheumatoid arthritis. The patient had previously participated in celecoxib clinical trial #N49-96-02-023, during which the patient had received celecoxib 100 mg BID, 200 mgBID, 400 mg BID, naproxen 500 mg or placebo BID. After the patient successfully completed this study, he was entered into the long-term safety study and began taking celecoxib 200 mg BID on February 6, 1997. Dosage was adjusted to 300 mg BID 42 days later, on March 20 1997, and again adjusted to 400 mg BID 49 days later, on May 8,1997. Three hundred six days after last dose adjustment, on March 10, 1998, the patient expired in his home due to cardiopulmonary arrest as a consequence of coronary artery disease. Concomitant medications included methotrexate sodium, multivitamin, folic acid, diltiazem hydrochloride, inadapamide, mononitrate, and baby aspirin. Study medication was continued until the time of death.

**8. Patient No. US0024-0004** (Myocardial Infarction) was a 59 year old male with a history of cardiomegaly, lumbar and cervical spine surgery, umbilical hernia repair, peripheral edema, hypertension, hip replacement, spinal stenosis, muscle spasm, elevated creatine phosphokinase, two pack per day smoker, obesity and RA. The patient had previously participated in the N49-96-02-012 clinical trial during which he received celecoxib 400 mg BID for four weeks. One hundred and forty days after successfully completing this study, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID on 31 July 1996. Dosage was increased to 300 mg BID 42 days later, on 11 September 1996, and to 400 mg BID 21 days later on 2 October 1996. Two hundred and nine days after the last adjustment, on 29 April 1997, the patient suddenly collapsed while at a horse race track. Following an unsuccessful resuscitation attempt, the patient was subsequently pronounced dead in the emergencyroom as a result of an acute myocardial infarction due to hypertensive heart disease. Examination on the body after death revealed distinguishable earlobe creasing and edema to the ankles. There was no indication of injury. No autopsy was performed.Concomitant medications included aurothioglucose, prednisone and lisinopril. (The Searle Medical Monitor elected to code this event as "sudden death" until more information about the evidence of M.I. was available).

**9. Patient No. US0027-0004** (Anterior Myocardial Infarction) was a 66year old male with a history of tinnitus, hypertension, benign prostatic hypertrophy, mechanical low back pain, Baker's cyst, right knee arthrotomy, lipoma of the right shoulder, cholelithiasis, exogenous obesity, anemia, choroidal nevus, and RA. The patient had previously participated in the N49-96-02-012 clinical trial during which he had received placebo. After successfully completing this study, he was entered the long-term safety study and began taking celecoxib 200 mg BID on 18 July 1996. Dosage was increased to 300 mg BID thirteen days later on 31 July 1996, and again increased to 400 mg BID twenty eight days later on 28 August 1996. Two hundred and eighty five days after the last adjustment on 9 June 1997, the patient developed chest pressure while at rest with associated diaphoresis that persisted for one hour. He went to the emergency room where an electrocardiogram was negative. Treatment included sublingual nitroglycerin and nitroglycerin paste with relief of his pain. Subsequent electrocardiogram revealed possible non-specific anterolateral T wave change and he was admitted for further evaluation on 10 June 1997. On admission, his blood pressure was (b)(4) with no abnormalities noted on physical examination. A cardiac catheterization (continued)

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performed that same day revealed significant disease of the left anterior descending coronary artery, 90% discrete stenosis, followed by a large first diagonal that had a (b)(4) Left ventriculography revealed moderately severe anterolateral hypokinesis with an ejection fraction around 45 to 50% overall. One day later on 11 June 1997, the patient underwent a percutaneous transluminal coronary angioplasty with implantation of a JR II intracoronary stent in the first diagonal and a J & J intracoronary stent in the left anterior descending. There were no residual stenoses. Post procedure, when his sheath was pulled, he developed some sinus bradycardia and associated hypotension, which was treated with no further sequelae. The patient had no further complaints of chest pain or shortness of breath and was discharged two days later on 13 June 1997. Treatment included ticlopidine, acetylsalicylic acid, atenolol, andranitidine. Study medication was discontinued, and the patient was terminated early from the study on 17 June 1997 due to taking the above medications. The patient was started on diclofenac that same day. On the night of 19 August 1997 (sixty-three days later after terminating from the study) the patient developed chest pressure. This persisted and he went to the emergency room early the following morning on 20 August 1997. Electrocardiogram showed acute anterior ST elevation. He was treated with thrombolytics. The chest pain continued and he was subsequently transferred to another hospital for further cardiac evaluation. On admission, lung sounds were diminished and heart rate and rhythm were regular with S1, S2, and S4 gallop. Peak creatine (b)(4) which was corrected (b)(4) (b)(4) Following admission the patient underwent an emergency left heart catheterization with coronary angiography due to continued chest pain. This showed hazy proximal left anterior descending with subtotal occlusion of diagonal and thrombus in the distal left anterior descending. The patient was started on abciximab and an intra-aortic balloon pump was then inserted. He developed a wide complete tachycardia requiring intubation and subsequent CPR. The patient was resuscitated. In the cath lab the patient vomited approximately (b)(4) of bright red blood and a gastroenterology consult was obtained. An acute GI hemorrhage was suspected either due to a Mallory-Weiss tear versus diclofenac induced surgery. It was also felt that anticoagulant therapy had contributed to the blood loss. Neurologically, the patient did not arouse post-code and developed mild clonic activity. On consultation, the neurologist felt that symptoms were indicative of a moderate to severe intracranial hypoxic event. The patient did not regain consciousness. He died the following day on 21 August 1997. Concomitant medications included folic acid, methotrexate, hydroxychloroquine, and verapamil.

**10. Patient No. US0042-0004** (Pulmonary Carcinoma) was a 77 year old female with a history of cardiomegaly, periodontal disease, hearing loss, hemorrhoids, breast cyst, myopia, chronic obstructive lung disease, smoker, pneumonia, shortness of breath and osteoarthritis. The patient had previously participated in celecoxibclinical trial #N49-96-02-022, during which she had received either placebo, celecoxib 50 mg BID, 100 mg BID, 200 mg BID or naproxen 500 mg BID. After successfully completing this study, she immediately entered into the long-term safety study and began taking celecoxib 100 mg BID on November 19, 1996. Dosage was adjusted to 200 mg BID 168 days later, on May 6, 1997. After another 288 days of treatment, on February 18, 1998, she was seen for her month 15 visit with complaints of increased shortness of breath and cough. She had completed a regimen of cefprozil on this same date. Chest x-ray was performed and showed a large infiltrate mass in the left lung. Computed tomography performed 5 days later, on February 23, 1998 confirmed alarge left hilar mass which appeared to have mediastinal invasion. Nine days later, on March 4, 1998, a diagnostic bronchoscopy with endobronchial biopsy was performed and was suggestive of a bronchogenic neoplasm with secondary atelectasis. Pathology report of the left upper lobe bronchial biopsies showed non small cell carcinoma (possible large cell undifferentiated carcinoma) of the left upper lobe of her lung. Study medication was discontinued on March 10, 1998, and the patient was withdrawn from the study on March 12, 1998. Twelve days later, on March 24, 1998, the patient was admitted for an exudative pleural effusion and a new onset of atrial fibrillation. She was treated with insertion of a chest tube and warfarin sodium. She was subsequently discharged onMarch 31, 1998. Eleven days later, on April 11, 1998, the patient was readmitted withincreasing shortness of breath. She was noted to have complete white out of her left lung. A chest tube was inserted, and 2 liters of fluid were removed. Other treatment included pain medication, antibiotics, steroids, breathing treatments, a radiation substantially, and she expired 4 days later, on April 15, 1998. Concomitant medications included triamcinolone acetonide, albuterol and calcium carbonate.

(continued)

**11. Patient No. US0052-0043** (Coronary Thrombosis) was an 84 year old female with a history of hypertension, coronary artery disease, cigarette smoking, occasional indigestion, atherosclerosis, hyperlipidemia, adult onset diabetes mellitus, anxiety attack, bronchitis, depression, and RA. The patient had previously participated in the N49-96-02-023 clinical trial during which she received celecoxib 400 mg BID. After being withdrawn early from this study due to a nosebleed, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID on 10 April 1997. Dosage was increased to 300 mg BID 14 days later, on 24 April 1997. One hundred and seventy nine days later, on 20 October 1997, the patient died of a coronary thrombosis; a contributing cause of death was considered to be chronic obstructive pulmonary disease. Concomitant medications included alprazolam, ipratropium, albuterol, salmeterol xinafoate, vitamin E, baby aspirin, glipizide, Triavil, pentoxifylline, enalapril maleate, and lovastatin. The Investigator was uncertain of the association of the event with the study drug.

**12. Patient No. US0053-0001** (Ventricular Fibrillation, Myocardial Infarction, Coronary Artery Disease) was an 80 year old male with a history of cataracts, spinal stenosis, cardiomyopathy, cardiac arrhythmia, angina, mild congestive heart failure, pneumonia, colon polyps, irritable bowel syndrome, constipation, hyperlipidemia, gastroduodenal ulcer, benign prostatic hypertrophy, meniscectomy, hypothyroidism, gout, hypertension, depression and OA. The patient had previously participated in the N49-96-02-020 clinical trial during which he received celecoxib 100 mg BID. After withdrawing early from this study due to treatment failure, the patient was entered into the long-term safety study and began taking celecoxib 100 mg BID on 11 September 1996. Dosage was increased to 200 mg BID 14 days later, on 25 September 1996. One hundred and thirty days later, on 2 February 1997, the patient woke up " not feeling well". After eating breakfast, the patient left the table, collapsed and died. Death certificate reveals cause of death to be cardiorespiratory arrest due to ventricular fibrillation, acute myocardial infarction and coronary artery disease. Concomitant medications included methylcellulose, levothyroxine, allopurinol, propoxyphene, gemfibrozil, furosemide, digoxin, diltiazem, potassium chloride, losartan, sertraline and psyllium.

**13. Patient No. US0058-0018** (Coronary Artery Disorder) was a 60 year old female with a history of allergic rhinitis, nasal congestion, refraction disorder, bilateral middle finger numbness, asthma, hemorrhoids, stress incontinence, cystocele,total abdominal hysterectomy and bilateral salpingo-oophorectomy, post-menopausal, intermittent back pain, right great toe fracture, lumbar laminectomy, bilateral calcaneal spurs, intermittent eczema, hypercholesterolemia, exogenous obesity, allergies to adhesive tape and amoxicillin, inhalant allergies, and OA. The patient had previously participated in the N49-96-02-021 clinical trial during which she received celecoxib mg BID. After successfully completing this study, the patient was entered into the long-term safety study and began taking celecoxib 100 mg BID on 20 February 1997. Dosage was increased to 200 mg BID 14 days later on 6 March 1997. One hundred and forty six days later, on 30 July 1997 the patient was found dead by her son. An autopsy performed one day later, on 31 July 1997, revealed arteriosclerotic cardiovascular disease with severe narrowing of the left anterior descending coronary, right coronary artery by atherosclerosis, and severe atherosclerosis of the aorta. No evidence of a recent or old myocardial infarction was noted. Hashimoto's thyroiditis and cholesterolosis of the gallbladder were also seen on autopsy. The death certificate shows the patient died of ischemic heart disease. Concomitant medications included Naldecon, pravastatin, estrogen, calcium carbonate, and allergy injection.

**14. Patient No. US0066-0004** (Respiratory Insufficiency, Pulmonary Carcinoma, Treatment Emergent Surgery) was a 60 year old male with a history of tonsillectomy, seasonal allergies, sleep apnea, hypertension, appendectomy, cholecystectomy, obesity, peripheral edema, adult onset diabetes mellitus, skin rash, proteinuria/gold therapy, excision of eyelid polyps, toe surgery, allergy to penicillin, excoriated insect bites, hyperlipidemia, hypothyroidism, chronic obstructive lung disease, tobacco use and RA. The patient had previously participated in the N49-96-02-023 clinical trial during which he received placebo. After being withdrawn early from this study due to treatment failure, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID on 11 November 1996. Dosage was increased to 300 mg BID 15 days later, on 27 December 1996. Eighty three days later, on 20 March 1997, the patient complained of chest pain. The Investigator referred the patient to his primary physician, who started the patient on clarithromycin for possible pneumonia and did a chest x-ray. Twenty six days later, on 15 April 1997, the patient was hospitalized for a lung mass which was seen on the chest x-ray. Three days following hospital admission, on 18 April 1997, 4000 cc of fluid was aspirated from the patient's lungs. Cell differential of this fluid returned cancer cells. The diagnosis of adenocarcinoma of the lung was made and a scan showed metastasis of the liver. Thirteen days following admission, on 28 April 1997, a thoracotomy was performed. The patient was mechanically ventilated postoperatively. Seven days later, on 5 May 1997, the patient expired due to respiratory failure secondary to carcinoma of the left lung. Concomitant medications included diltiazem, glipizide, gemfibrozil, levothyroxine, docusate, terfenadine, methotrexate, phentermine, fenfluramine, anti-fungal cream and continuous positive airway pressure oxygen. Study drug was discontinued on 15 April 1997. The patient never recovered

**15. Patient No. US0073-0060** (Respiratory Insufficiency, Cardiac Failure) was an 85 year old female with a history of removal of benign throat tumor, hypertension, peptic ulcer disease, cholecystectomy, cigarette smoking, post-menopause, osteoporosis, right hip replacement, hypothyroidism, bilateral cataracts, lens implants,and RA. The patient had previously participated in the N49-96-02-023 clinical trial during which she received placebo. After being withdrawn early from this study due to treatment failure, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID on 10 March 1997. Dosage was increased to 300 mg BID four days later, on 14 March 1997 and to 400 mg BID 11 days later, on 25 March 1997. Twohundred and twenty eight days after dose adjustment, on 8 November 1997, the patient was hospitalized for unknown reasons. The patient died 12 days later, on 20 November 1997 of respiratory secondary to congestive heart failure. Concomitant medications included sulfasalazine, levothyroxine sodium, alendronate sodium, lisinopril, furosemide, and potassium chloride. Study drug was interrupted during hospitalization.

**16. Patient No. US0073-0189** (Myocardial Infarction) was a 71 year old female with a history of sleep disturbance, hypertension, irregular heart rate, cholecytecomy, appendectomy, ovarian cyst removed, benign breast cyst removed, cataracts, post-menopausal, anemia, hyperglycemia, hypercholesterolmia, hyperuricemia, and rheumatoid arthritis. The patient had previously participated in celecoxibclinical trial #N49-96-02-022, during which the patient had received either placebo, celecoxib 100 mg BID, 200 mg BID, 400 mg BID or naproxen 500 mg BID. After terminating early due to treatment failure, she was entered into the long-term safety study and began taking celecoxib 200 mg BID on November 21, 1997. Seventeen days later, on December 8, 1997, dosage was adjusted to 400 mg BID. Seventeen days later, on December 28, 1997, the patient began experiencing jaw pain that radiated to the chest. The patient was hospitalized with a possible myocardial infarction. Initial cardiac enzymes were elevated. An electrocardiogram revealed septal and lateral wall changes. Treatment included subcutaneous heparin sodium, nitroglycerin, metoprolol tartrate, and warfarin sodium. Three days after admission, on December 31, 1997, the patient died due to complications from a myocardial infarction. Concomitant medications included methotrexate, folic acid, enalapril, calcium carbonate, vitamin E, lorazepam, multivitamin, digoxin, and prednisolone acetate.

**17. Patient No. US0087-0100** (Sepsis, Pneumonitis, Respiratory Insufficiency) was a 66 year old male with a history of hypertension, gastrointestinal upset related to anti-inflammatory medications, reflux esophagitis, gastritis, benign cyst on left hip, osteoporosis, dermatitis, heat rash, diabetes, positive Helicobacter pylori, right medial menisectomy, crush injury to left hand and remote history of peptic ulcer disease, allergy to penicillin, and rheumatoid arthritis. The patient had previously participated in celecoxibclinical trial #N49-97-02-023, during which the patient had received celecoxib 100 mg BID, 200 mg BID, 400 mg BID, naproxen 500 mg BID or placebo BID. After terminating early from this study due to treatment failure, he was entered into the long-term safety study, N49-96-02-024, and began taking celecoxib 200 mg BID on May 6, 1997. Dosage was increased to 300 mg BID, 14 days later, on May 20, 1997 and increased again to 400 mg BID, 4 days after that, on May 24, 1997. One hundred and seventy-four days after dose adjustment on November 14, 1997, the patient was admitted to the intensive care unit for complaints of shortness-of-breath, dyspnea, left sided weakness and elevated blood pressure. A CAT scan of the lungs showed alveolar edema, chest x-ray revealed peripheral pulmonary fibrosis, presumably secondary to rheumatoid arthritis or long-term methotrexate therapy, and changes consistent with pulmonary edema. And electrocardiogram revealed sinus tachycardia with ST and T sagging in the lateral leads, and a suggestion of left atrial hypertrophy. A CAT scan of the head was negative. Blood cultures revealed enterococcal species. Physical exam was remarkable for crackles in bilateral lung fields almost to the scapular level and slight left arm and leg weakness with slightly diminished reflexes bilaterally. According to the study coordinator, the patient's blood pressure had been elevated to at least (b)(4) at his past few visits and he had been advised to see his primary physician. The patient was started on enalapril maleate, furosemide, and digoxin. Additional treatment for this event included Humulin Insulin, multiple antibiotics, Ventolin, Atrovent, Heparin and famotidine, tracheostomy and mechanical ventilation. The patient died 29 days later, on December 2, 1997. The cause of death was determined to be respiratory failure, overwhelming sepsis and the interstitial pneumonitis. Concomitant medications included hydroxychloroquine sulfate, folic acid, glyburide, omeprazole, metformin hydrochloride, calcium and methotrexate. Study medication was interrupted during hospitalization.

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**18. Patient No. US0110-0006** (Myocardial Infarction) was a 61 year old female with a history of fluid retention, hyperlipidemia, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, tobacco use, triple bypass surgery, arrhythmia, abdominal aortic aneurysm, hysterectomy, thrombocytosis and rheumatoid arthritis. The patient had previously participated in Searle study #N49-96-02-022, during which she received either placebo, celecoxib 100 mg BID, 200 mg BID, 400 mg BID or naproxen 500 mg BID. After successfully completing this study, on December 17, 1996, the patient was entered into the long-term safety study and began taking celecoxib 200 mg BID. Dosage was adjusted to 300 mg BID 17 days later, on January 3, 1997, and again to 400 mg BID 35 days after that, on February 7, 1997. Two hundered and twenty days after the last dose adjustment, on September 15, 1997, the patient underwent femoral bypass surgery due to a foot ulcer that was caused by poor circulation. The patient was discharged 3 days later, on September 18, 1997. Eleven days later, on September 29, 1997, the patient was re-hospitalized with complaints of chest pain. The patient underwent cardiac catheterization and angioplasty with stent placement. The patient was discharged 31 days later, on October 30, 1997. Seventy-seven days later, on January 13, 1998, the patient suffered a myocardial infarction and died. The patient's brother had died earlier in the week. Concomitant medications included prednisone, digoxin, pravastatin sodium, acetylsalicylic acid, furosemide, pentoxifylline, and multivitamins.

**19. Patient No. US0116-0042** (Arterial Dissection, Aneurysm) was a 78 year old female with a history of cataracts, lens implants, hypertension, supraventricular tachycardia, angioplasty, appendectomy, hiatal hernia, post-menopause, bilateral metatarsophalangeal repair, allergies to piroxicam and gold, and rheumatoid arthritis. The patient had previously participated in celecoxib clinical trial # N49-96-02- 022, during which the patient had received either placebo, celecoxib200 mg BID on September 25, 1997. After 88 days of treatment, on December 22, 1997, the patient was hospitalized with an ascending aortic aneurysm and developed a dissection which was confirmed on repeat CT scanning. Preoperative echocardiogram revealed moderately severe aortic stenosis with a peak gradient of 42. On December 24, 1997, the patient underwent an aortic valve replacement with a (b)(4) [redacted] valve and ascending aorta and hemi-arch replacement with (b)(4) [redacted] graft utilizing circulatory arrest and hypothermia. During the procedure, the patient began bleeding from the anterior portion of the proximal anastomosis and developed left ventricular aortic discontinuity from this area. Massive bleeding ensued. Attempts to repair this were unsuccessful and the patient was pronounced dead. The death certificate revealed the cause of death as type I ascending (aortic) arch dissection, artherosclerotic coronary artery disease and critical aortic stenosis. Concomitant medications included sulfasalazine, diltiazem hydrochloride-sustained release, thyroid, Ascriptin, medroxyprogescerone acetate, conjugated estrogens, and digoxin. Study medication was interrupted one day prior to hospitalization.

**20. Patient No. US0121-0052** (Sepsis, Pneumonia, Myocardial Infarction) was a 52 year old male with a history of tinnitus, recurring sore throats, decreased hearing, sinus trouble, sores in mouth, glasses, pain behind eyes, depression, headaches, vertigo, fainting spells, occasional chest pain, influenza, cough, chronic obstructive airway disease, pneumonia, obesity, hernia repair, appendectomy, H. pylori, hemorrhoids, gastritis, pedal edema, leg cramps, bursitis, brittle nails, skin rash, hypoglycemia, diabetes mellitus, allergies to penicillamine and cyclosporin, and RA. The patient had previously participated in the N49-96-02-022 clinical trial during which he had received celecoxib 100 mg BID. After successfully completing this study, he was entered into the long-term safety study and began taking celecoxib 200 mg BID on 29 September 1997. Fourteen days later, on 13 October 1997, dosage was increased to 300 mg BID. Four days after that on 17 October 1997, the patient presented with shortness of breath which had been present for one month, and had become significantly worse, and was admitted with respiratory distress. Physical examination revealed a blood pressure of (b)(4) [redacted] on dopamine, respiratory rate (b)(4) [redacted] which was decreased from 36 previously, and a temperature (b)(4) [redacted] Lung auscultation revealed crackles in the left base, and a trace of bipedal pitting edema. Pleural fluid and sputum grew Acinetobacter "pneumoniae." White blood cell count (b)(4) [redacted] admission. Complete blood differential count revealed a left shift with (b)(4) [redacted] The patient's blood urea nitrogen (b)(4) [redacted] neutrophilic predominance and glucose (b)(4) [redacted] Blood cultures grew a bacillus species. Electrocardiogram revealed sinus tachycardia with an incomplete right bundle branch block and small Q wave in lead (continued)

III with anterolateral ST changes consistent with possible ischemia. Chest x-ray showed cardiomegaly and a possible pleural effusion on the left. Treatment included intubation and subsequent ventilator support, thoracentesis, insertion of a Swan-Ganz, central venous pressure line, arterial line and Vas-Cath, dopamine in increasing doses, rescue doses of steroids, ceftriaxone, sodium, fluid replacement for dehydration and sepsis, phenylephrine hydrochloride drip, amikacin, and ofloxacin. The patient was found to have gram negative sepsis and pneumonia and subsequently expired one day later on 18 October 1997. According to the death certificate, the patient died of an acute myocardial infarction. No autopsy was done. Concomitant medications included methotrexate, prednisone, and folic acid as well as nasal continuous positive airway pressure. Study medication was continued up until the time of death.

**21. Patient No. US0139-0009** (Subarachnoid Hemorrhage) was a 57 year old female with a history of dyspepsia, hysterectomy, lumbar spinal fusion, and RA. The patient had previously participated in the N49-96-02-022 clinical trial during which she had received placebo. After successfully completing this study, she was entered into the long-term safety study and began taking celecoxib 200 mg BID on 26 August 1997. Twenty three days later on 18 September 1997, the patient was admitted with a grade V subarachnoid hemorrhage. On admission her right pupil was fixed and dilated and she had decerebrate posturing. Apparently, this had occurred at 4:30 in the morning, with onset of emesis and loss of consciousness at that time. She was subsequently intubated and received mannitol and was transferred by ambulance to the hospital. On examination her initial blood pressure was 200/80 and nitroglycerin paste was given to help lower this. Her Glasgow Coma Scale at the time of admission was 4T. A computerized tomography scan revealed diffuse subarachnoid hemorrhage with a large right sided temporal lobe clot; intraventricular hemorrhage; right to left shift; and extensive midbrain compression and swelling. The patient deteriorated and was pronounced brain dead later that same day. Concomitant medications included methotrexate, folic acid, sulfasalazine, and estrogen.

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## 7.1 Appendix Two: Serious Adverse Events related to renal function in the Celecoxib NDA Database

1) Acute Renal Failure There were two cases of acute renal failure (uremia) in celecoxib treated patients; one was due to repeated quinine use, the other associated with obstructive uropathy.

The first occurred in a 70-year-old female (047-US0033-0030) with a prior history of labile vascular hypertension, and urinary system disorders including urethral stenosis, urgency, and bladder spasms. Concomitant medications at the time of the event were: captopril, chlorpheniramine, docusate sodium, aspirin, estrogen, etidronate, fluconazole, dexamethasone, oxybutynin, pravastatin, quinine sulfate, and verapamil. Three weeks after initiating treatment with celecoxib 400 mg BID, she experienced leg cramps for which she took quinine and subsequently experienced headache and pruritus. One week later, she repeated a single dose of quinine and again experienced headache and pruritus, but also nausea, vomiting, diarrhea, chills, and confusion. Four days later she was hospitalized with a fever and a creatinine (b)(4) She was diagnosed with hemolytic uremic syndrome presumed due to quinine sulfate. Treatment included plasmapheresis, hemodialysis, and platelet transfusion.

The patient with acute renal failure associated with likely obstructive uropathy was a 65- year-old male (024-US0149-1490002), with a medical history of hypertension, depression, nocturia and RA. Concurrent medications included gold sodium thiomalate, terazosin, fosinopril, metoprolol, prednisone, and combination perphenazine and amitriptyline. The patient took celecoxib 100 mg BID for 12 weeks in a double-blind clinical RA trial. After successfully completing the trial, he was admitted to the long-term open-label trial. He was instructed to take celecoxib 200 mg BID, but for unknown reasons, he took only 100 mg BID. The patient returned for the Week 2 Visit and no abnormalities were noted. Four days after he was seen for his "Week 6" visit, his urine output decreased and he felt ill. This was approximately one week following an endoscopic procedure associated with anaesthesia. (b)(4) showed bilateral hydronephrosis. He was scheduled for cystoscopy and retrograde ureteroscopy and possible stent placement when he developed significant large volume diuresis with normalization of his renal function. He recovered and was discharged from the hospital five days later. One week later, his serum creatinine value was (b)(4) mg/dL and his BUN (b)(4) The Investigator felt there was a probable association between the event and study medication. The Searle Clinical Safety Committee considered the event not to be related to celecoxib because the radiographic evidence favored obstructive uropathy possibly secondary to prostatic enlargements.

2) Diuretic-induced hyponatremia/ hypokalemia There were two serious adverse events of diuretic-induced hyponatremia (one of which was principally coded as hypokalemia) that resulted in patients being hospitalized.

One of these patients was a 72-year-old female (024-US0033-0330007) with history of hypertension, venous insufficiency, hypercholesterolemia, and hypothyroidism. Concurrent medications included hydrochlothiazide, triamterene, verapamil, and calcium. This patient took celecoxib 300 mg BID for 14 days before discontinuing because of treatment failure. Two days after stopping celecoxib, she was hospitalized with a plasma sodium level of (b)(4) She was rehydrated with intravenous fluid and her plasma sodium returned to normal. Her hospital diagnosis indicated metabolic encephalopathy secondary to hyponatremia most likely due to diuretic therapy.

The other patient with hyponatremia (coded as hypokalemia) was a 78-year-old female (024-US0013-0130009) with a history of hypertension, urinary complaints such as nocturia and bladder suspension surgery, and elevated liver function tests. Concurrent medications included doxazosin, Moduretic and indapamide. The patient initiated treatment with celecoxib 200 mg BID and experienced sinusitis eight-and-one-half months later. She was treated with antibiotics but three days later she lost consciousness and was incontinent of urine. Following this syncopal episode, she vomited. She was taken to the hospital, where her serum potassium and sodium were found to be (b)(4) respectively. She was rehydrated with intravenous solution, treated with potassium, and indapamide was discontinued. Amoxicillin was continued to treat the sinusitis.

3) Renal Calculus Renal calculus occurred in one male and two female RA patients taking celecoxib 200 mg BID. The onset of occurrence ranged from 59 to 205 days. The 43-year-old male (024- US0001-0010016) had a prior history of bilateral total hip replacements. His only concurrent medication was Auranofin . He underwent a successful stenting procedure and was withdrawn from the study. The 58-year-old female (024-US0009-0090037) had a prior history of renal calculus. Concurrent medications were methotrexate and folic acid. She underwent a successful stenting procedure and continued in the study. The 27- year-old female (071-US0354-56553061) had a history of

seizure disorder, depression, and four miscarriages. Concurrent medications included prednisone and fluoxetine. She passed a kidney stone while receiving medical tx in the hospital and was withdrawn from study.

4) Cardiac Failure There were four cases of cardiac failure that were serious adverse events. Three of these patients were taking celecoxib at the time the event occurred. A 71-year-old male (024-US0006-0060001) with a history of heart disease, heart attack, pneumonia (including a recent episode), surgery for lung biopsy, hypertension, and RA experienced respiratory arrest and was hospitalized after 196 days of study medication (celecoxib 300 mg BID). He also experienced a cardiac arrest on the same day. He continued to take study medication and 76 days after this initial hospitalization, the patient experienced shortness of breath, left chest pain and was readmitted. Chest x-ray showed evidence of congestive heart failure. Treatment included supplemental oxygen, intravenous furosemide, and amlodipine. Concomitant medications included triamcinolone acetonide, potassium chloride, digoxin, and bumetanide. The patient was discharged three days later and the patient recovered.

A 76-year-old male (060-US0198-0214) with a history of atrial fibrillation, congestive heart failure, hypertension, diabetes and OA was hospitalized seven days after initiating therapy with celecoxib 100 mg BID after experiencing increasing paroxysmal nocturnal dyspnea, orthopnea, and dyspnea. Concomitant medications included digoxin, metoprolol, furosemide, flecainide acetate, potassium chloride, and aspirin. The patient was treated with nitroglycerin as needed and was discharged three days later with a final diagnosis of angina. The patient was discharged three days later and the patient recovered. An 81-year-old female (0210-US0113-0139) with a history of OA, cerebral vascular accident, angina, hypertension, arrhythmias, congestive heart failure and coronary artery disease was hospitalized 52 days after initiating therapy with celecoxib 200 mg BID for congestive heart failure. Concomitant medications included furosemide, aspirin, doxazosin mesylate, nitroglycerin and potassium chloride. The patient was treated with losartan, Prinivil, and digoxin and has recovered.

5) Aggravated Hypertension There were three cases of aggravated hypertension and one case of hypertension in patients taking celecoxib that were serious adverse events.

A 71-year-old female (024-US0005-00500022) with a history of hypertension and heart murmur was hospitalized for vertigo and nausea after taking celecoxib 200 mg BID for twelve weeks and subsequently celecoxib 100 mg BID for 10 days. Her blood pressure was found at that time to be (b)(4) and she had a normal physical examination. She was about to be discharged when she had a similar episode of vertigo. At that time, her blood pressure (b)(4) Sublingual nifedipine was given, which brought the blood pressure back to normal. Final diagnosis was calcified meningioma, which did not require surgery. Concomitant medications included verapamil and aspirin.

A 62-year-old female (071-US0016-76132005) with a history of chronic hypertension was hospitalized after 51 days of treatment with celecoxib 200 mg BID. According to the patient, her blood pressure was (b)(4) Concomitant medications included betaxolol and doxazosin

A 40-year-old female (062-US0265-54241602) with a history of malignant hypertension, chest pain, Type II diabetes mellitus was hospitalized after 25 days of taking celecoxib 200 mg BID complaining of chest pain. Her blood pressure was (b)(4) Renal arteriogram revealed a unilateral (b)(4) renal artery stenosis. Concomitant medications included clonidine, lisinopril and ticlopidine. Lisinopril was discontinued and she was placed on losartan and metoprolol. Forty-nine days later the patient was readmitted with a blood pressure of (b)(4) Isosorbide was added to her treatment regimen with marked improvement noted.

A 54-year-old female (022-US0114-0345) with a history of hypertension, chest pain and type II diabetes was hospitalized after 88 days of taking celecoxib 400 mg BID. She was severely hypertensive and was diagnosed with hypertensive encephalopathy.

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