

**Table 76. Incidence of Liver Function Test Abnormalities : Placebo- and Active-Controlled 12-Week Arthritis Trials**

| Clinical Laboratory Parameter | Celecoxib<br>100 and 200 mg BID |     | Placebo            |     | Naproxen<br>500 mg BID |     |
|-------------------------------|---------------------------------|-----|--------------------|-----|------------------------|-----|
|                               | No. of Patients(a)              | %   | No. of Patients(a) | %   | No. of Patients(a)     | %   |
| Total Bilirubin               | 2181                            |     | 1077               |     | 1069                   |     |
| >26 µmol/L                    |                                 | 0.4 |                    | 0.4 |                        | 0.1 |
| >35 µmol/L                    |                                 | 0.1 |                    | 0.2 |                        | 0   |
| AST(b)                        | 2188                            |     | 1080               |     | 1072                   |     |
| >75 U/L                       |                                 | 0.1 |                    | 0.2 |                        | 0.2 |
| >200 U/L                      |                                 | 0   |                    | 0.2 |                        | 0.1 |
| ALT(c)                        | 2188                            |     | 1080               |     | 1072                   |     |
| >75 U/L                       |                                 | 0.6 |                    | 0.8 |                        | 0.6 |
| >200 U/L                      |                                 | 0   |                    | 0.1 |                        | 0.1 |
| Alk Phos(d)                   | 2181                            |     | 1079               |     | 1071                   |     |
| >200 U/L                      |                                 | 0.1 |                    | 0   |                        | 0   |
| >500 U/L                      |                                 | 0   |                    | 0.1 |                        | 0   |
| Albumin                       | 2180                            |     | 1077               |     | 1068                   |     |
| <30 g/L                       |                                 | 0.8 |                    | 0.6 |                        | 0.1 |
| <20 g/L                       |                                 | 0   |                    | 0   |                        | 0   |

- a) No. of patients with normal values at Baseline  
 b) AST; aspartate transaminase  
 c) ALT; alanine transaminase  
 d) Alk Phos; alkaline phosphatase

*6.3.10.2.5 Hepatically Impaired Subjects: Study 016*

The PK parameters, safety, and tolerability of a single dose of celecoxib 100 mg and after eight multiple doses of celecoxib 100 mg BID were examined in an open-label study of 23 patients with mild or moderate hepatic impairment based on the Child-Pugh Classification System.

There were no laboratory values for which the mean change from Baseline to Post-treatment was statistically significantly different for the mildly and moderately hepatically impaired subjects. When the mildly and moderately hepatically impaired subjects were analyzed separately, only mean total bilirubin levels decreased significantly from Baseline to Post-treatment within the group of mildly impaired subjects.

*6.3.10.2.6 Summary and Conclusions*

The results indicate that celecoxib is not associated with alterations in liver function or with adverse events due to liver or biliary tract disease. Celecoxib is metabolized in the

liver, and while clearance of celecoxib is reduced in the presence of moderate liver disease, the tolerability of the drug is not affected. Liver function test abnormalities were rare, and seen only at rates similar to or less than placebo and significantly less than NSAIDs.

### 6.3.10.3 Renal Effects

#### 6.3.10.3.1 Adverse Events

The incidence of adverse events related to renal function that occurred at an incidence 0.5% or greater in patients who were enrolled into the North American Controlled Arthritis Trials are summarized in Table 77. Peripheral edema and hypertension were the most frequently reported adverse events.

**Table 77. Renal Adverse Events as Reported by the Investigator with an Incidence  $\geq 0.5\%$  in Any Treatment Group: North American Controlled Arthritis Trials**

| Adverse Event           | Placebo | Celecoxib    |               |              |               |               | NSAID |
|-------------------------|---------|--------------|---------------|--------------|---------------|---------------|-------|
|                         |         | 50 mg<br>BID | 100 mg<br>BID | 200 mg<br>QD | 200 mg<br>BID | 400 mg<br>BID |       |
| No. treated             | 1864    | 690          | 1779          | 453          | 1914          | 615           | 2098  |
| Any renal event         | 2.5     | 3.6          | 2.9           | 4.4          | 5.6           | 5.5           | 4.1   |
| Generalized edema       | 0.0     | 0.1          | 0.1           | 0.2          | 0.1           | 0.3           | 0.5   |
| Peripheral edema        | 1.1     | 2.2          | 1.5           | 2.9          | 2.6           | 2.4           | 2.1   |
| Hypertension            | 0.3     | 0.3          | 0.6           | 0.2          | 1.0           | 0.5           | 0.7   |
| Aggravated hypertension | 0.4     | 0.0          | 0.4           | 0.9          | 0.6           | 0.7           | 0.3   |

\* All numbers are percentages of patients unless otherwise specified.

The incidence of peripheral edema associated with celecoxib was not dose related. Generalized edema was more often observed with the NSAIDs when compared to placebo or celecoxib. The incidence of hypertension or aggravated hypertension with celecoxib was similar to placebo and NSAIDs and no relationship to the administered dose of celecoxib was evident.

A comparison of statistically significant differences in the incidence of renal adverse events with the recommended therapeutic doses of celecoxib and either placebo or NSAIDs is presented in Table 78. The incidence of peripheral edema with celecoxib was significantly greater than placebo. The incidence of peripheral edema with the celecoxib

was comparable to NSAIDs, however; the incidence of generalized edema with celecoxib was significantly less than NSAIDs and comparable to placebo treatment.

**Table 78. Analysis of Renal Adverse Events between Celecoxib and Placebo or NSAIDs**

| Adverse Event           | Celecoxib* | Placebo | p Value | Celecoxib* | NSAIDs | p Value |
|-------------------------|------------|---------|---------|------------|--------|---------|
| No. treated             | 3512       | 1864    | -       | 2890       | 2098   | -       |
| Any renal event         | 5.6        | 3.6     | 0.002   | 6.1        | 4.8    | -       |
| Generalized edema       | 0.1        | 0.0     | -       | 0.1        | 0.5    | 0.031   |
| Peripheral edema        | 2.1        | 1.1     | 0.007   | 2.3        | 2.1    | -       |
| Hypertension            | 0.6        | 0.3     | -       | 0.8        | 0.7    | -       |
| Aggravated hypertension | 0.6        | 0.4     | -       | 0.6        | 0.3    | -       |

Data are expressed in percentages of patients (except for p values).

\*Column combines celecoxib 100 mg BID, 200 mg QD, and 200 mg BID.

An analysis of weight gain and blood pressure changes for patients with peripheral edema who were studied in the North American 12-Week Placebo- and Active-Controlled Arthritis Trials is shown in Table 79. The higher incidence of peripheral edema in celecoxib patients when compared to placebo patients was not associated with a corresponding significant change in mean body weight or blood pressure. Additionally, the incidence of patients with peripheral edema who gained one kilogram or more in body weight was similar across the treatment groups.

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**Table 79. Weight Gain and Blood Pressure Effects for Patients with Peripheral Edema: North American 12-Week Placebo- and Active-Controlled Arthritis Trials**

|  | Placebo         | Celecoxib<br>50-400 mg BID | Naproxen<br>500 mg BID |
|--|-----------------|----------------------------|------------------------|
|  | N=1136          | N=3380                     | N=1099                 |
| Incidence of peripheral edema (% of patients)  | 1.1%            | 2.5%*                      | 2.2%*                  |
| Percent of patients with peripheral edema and a weight gain $\geq 1$ kg                            | 0.5%            | 0.7%                       | 0.8%                   |
| Mean weight change in patients with peripheral edema (kg; mean $\pm$ SE)                           | 0.43 $\pm$ 0.71 | 0.27 $\pm$ 0.34            | 0.64 $\pm$ 0.49        |
| Mean weight change in patients without peripheral edema (kg; mean $\pm$ SE)                        | 0.13 $\pm$ 0.15 | 0.26 $\pm$ 0.05            | 0.27 $\pm$ 0.08        |
| Mean change in diastolic blood pressure in patients with peripheral edema (mmHg; mean $\pm$ SE)    | -1.3 $\pm$ 4.2  | -0.5 $\pm$ 1.3             | 0.5 $\pm$ 1.5          |
| Mean change in diastolic blood pressure in patients without peripheral edema (mmHg; mean $\pm$ SE) | -1.0 $\pm$ 0.3  | -0.5 $\pm$ 0.2             | -0.4 $\pm$ 0.3         |

\* Significantly different from placebo;  $p < 0.05$

*6.3.10.3.2 Adverse Events Causing Withdrawal*

Table 80 summarizes the incidence of withdrawals due to renal-related adverse events in the North American Controlled Arthritis Trials. The incidence of withdrawal due to edema or hypertension was low and no evidence for either dose-related or treatment-related effects was evident. Other reasons for withdrawal included the occurrence of increased creatinine in one patient treated with celecoxib 50 mg BID, one patient receiving celecoxib 200 mg BID, and one NSAID-treated patient. Two patients, one receiving placebo and the other celecoxib 200 mg BID, discontinued study participation due to renal calculus. Two patients receiving placebo discontinued treatment due to hematuria or abnormal renal function. Finally, one patient receiving celecoxib 400 mg BID withdrew as a result of uremia and hyperkalemia.

**Table 80. Incidence of Renal-Related Adverse Events Causing Withdrawal: North American Controlled Arthritis Trials**

| Adverse Event           | Placebo | Celecoxib    |               |              |               |               | NSAID |
|-------------------------|---------|--------------|---------------|--------------|---------------|---------------|-------|
|                         |         | 50 mg<br>BID | 100 mg<br>BID | 200 mg<br>QD | 200 mg<br>BID | 400 mg<br>BID |       |
| No. treated             | 1864    | 690          | 1779          | 453          | 1914          | 615           | 2098  |
| Any renal event         | 0.2     | 0.1          | 0.2           | 0.0          | 0.4           | 0.5           | 0.2   |
| Hypertension            | 0       | 0            | <0.1          | 0            | 0.1           | 0             | <0.1  |
| Aggravated hypertension | 0       | 0            | 0             | 0            | 0.2           | 0             | 0     |
| Generalized edema       | 0       | 0            | 0             | 0            | 0             | 0.2           | <0.1  |
| Peripheral edema        | <0.1    | 0            | 0             | 0            | 0             | 0.2           | <0.1  |

Data are expressed as percent of patients

#### 6.3.10.3.3 Serious Adverse Events

In the North American Controlled Arthritis Trials, there were 10 patients with serious adverse events related to renal function. Cardiac failure occurred in one placebo-treated patient and pyelonephritis occurred in a patient receiving ibuprofen. In celecoxib-treated patients, the following serious adverse events occurred: hypertension or aggravated hypertension (three patients), cardiac failure (two patients), renal calculus (two patients), and quinine-induced uremia (one patient).

Thirteen renal-related serious adverse events occurred in the North American Long-term Open Label Arthritis Study resulting in an incidence of 5 events per 1000 patient-years of exposure. This compares with an incidence of 7 events per 1000 patient-years for serious renal-related adverse events in patients receiving celecoxib in the controlled arthritis trials. In the North American Long-term Open Label Arthritis Study, there was one case of acute renal failure associated with obstructive uropathy, three cases of cardiac failure, two cases of renal calculus, one patient with aggravated hypertension, one occurrence of diuretic-induced hyponatremia, one case of hydronephrosis, two patients with pyelonephritis, one patient with renal colic and one patient with hypokalemia.

#### 6.3.10.3.4 Clinical Laboratory Results

Table 81 displays incidence of clinical laboratory abnormalities related to renal function occurring in the North American 12-Week Placebo- and Active-Controlled Arthritis Trials (Studies 020, 021, 022, 023, and 054). Extreme changes in renal-related clinical laboratory results were infrequent and differences across the treatment groups were

generally not evident. Moderate abnormalities in renal-related laboratories were more common. The incidence of moderate changes in serum sodium, chloride and potassium were higher with celecoxib and naproxen than with placebo. Treatment-related effects were not observed between celecoxib and placebo for all other renal-related clinical laboratory parameters.

**Table 81. Incidence of Clinical Laboratory Abnormalities Related to Renal Function: North American 12-Week Placebo- and Active-Controlled Arthritis Trials**

| Parameter  | Celecoxib<br>100 mg and 200 mg BID |            | Placebo            |            | Naproxen<br>500 mg BID |            |
|--|------------------------------------|------------|--------------------|------------|------------------------|------------|
|  | No. of Patients(a)                 | %          | No. of Patients(a) | %          | No. of Patients(a)     | %          |
| BUN<br>>9.3 mmol/L<br>>14.3 mmol/L                     | 2122                               | 3.3<br>0.1 | 1042               | 1.3<br>0   | 1036                   | 6.1<br>0.1 |
| Creatinine<br>> 176.8 µmol/L<br>> 265.2 µmol/L         | 2189                               | 0.1<br>0   | 1080               | 0<br>0     | 1072                   | 0<br>0     |
| Sodium<br><135 mmol/L<br><120 mmol/L                   | 2060                               | 6.3<br>0   | 1009               | 4.3<br>0   | 1004                   | 7.4<br>0   |
| Potassium<br>>5.0 mmol/L<br>>6.0 mmol/L                | 2063                               | 5.1<br>0   | 1037               | 2.3<br>0   | 1020                   | 5.8<br>0   |
| Chloride<br>>110 mmol/L<br>>130 mmol/L                 | 2101                               | 8.6<br>0   | 1031               | 4.9<br>0   | 1025                   | 8.3<br>0   |
| Calcium<br><1.7 mmol/L or >15% decrease<br><2.0 mmol/L | 2183                               | 0<br>0.3   | 1079               | 0<br>0     | 1070                   | 0<br>0.5   |
| Phosphate<br><0.97 mmol/L<br><0.32 mmol/L              | 1868                               | 20.1<br>0  | 920                | 17.2<br>0  | 900                    | 30.8<br>0  |
| Uric Acid<br><148.7 µmol/L<br><119 µmol/L              | 2056                               | 0.8<br>0.1 | 1003               | 0.5<br>0.2 | 978                    | 0.7<br>0.1 |
| Urine pH<br>>8<br>>8.5                                 | 2135                               | 0<br>0     | 1032               | 0<br>0     | 1040                   | 0<br>0.2   |
| Urine Protein<br>Trace<br>1+ (300 mg/24/h)             | 2071                               | 2.6<br>1.2 | 1006               | 2.6<br>1.3 | 1016                   | 3.8<br>0.6 |
| Urine Glucose<br>Trace<br>1+ (1 g/24/h)                | 2089                               | 0.9<br>2.4 | 1017               | 0.9<br>1.6 | 1012                   | 0.5<br>1.3 |
| Urine RBC<br>>5/hpf<br>>10/hpf                         | 2043                               | 2.1<br>4.2 | 976                | 1.8<br>3.7 | 991                    | 2.8<br>4.3 |

a) No. of patients with normal values at Baseline

6.3.10.3.5 *Effects on Blood Pressure*

In the North American Placebo- and Active-Controlled 12-Week Arthritis Trials, mean blood pressure decreased slightly from Baseline to Final Visit in all treatment groups (Table 82). Although there were statistically significant differences between celecoxib 100 and 200 mg BID and placebo for change in systolic and diastolic blood pressure ( $p < 0.001$  and  $p = 0.017$ , respectively), the differences were small and of no clinical significance. There was no pattern of increasing blood pressure with increasing celecoxib doses. Among patients in the North American Placebo- and Active-Controlled 12-Week Arthritis Trials, there was no statistically significant difference in the mean change in blood pressure from Baseline to Final Visit between celecoxib 400 mg BID and NSAIDs. There was a statistically significant difference between celecoxib 400 mg BID and placebo ( $p = 0.021$ ), but this difference was small (-0.5 mmHg compared to -2.1 mmHg) and not considered clinically meaningful.

**Table 82. Analysis of Blood Pressure Between Celecoxib and Placebo or NSAID: North American Placebo- and Active-Controlled 12-Week Arthritis Trials**

| Laboratory Value                                       | Celecoxib*<br>(N=4410) | Placebo<br>(N=2194) | p-value | Celecoxib*<br>(N=4410) | NSAID<br>(N=2150) | p-value |
|--|------------------------|---------------------|---------|------------------------|-------------------|---------|
| <b>Mean Change from Baseline to Final Visit – mmHg</b> |                        |                     |         |                        |                   |         |
| Systolic BP  | -0.5                   | -1.9                | <0.001  | -0.5                   | -0.9              | -       |
| Diastolic BP   | -0.4                   | -1.0                | 0.017   | -0.4                   | -0.5              | -       |

\*Column combines celecoxib 100 and 200 mg BID.

Blood pressure results from the North American Long-term Open Label Arthritis Study demonstrated that celecoxib did not markedly affect blood pressure with treatment up to 15 months (Table 83). The greatest mean change from baseline in blood pressure was reported at Week 2: -1.2/-0.6 mmHg.

**Table 83. Change from Baseline in Blood Pressure: North American Long-term Open Label Arthritis Study**

| Laboratory Value                        | Celecoxib*        |                   |                     |                     |                     |                     |                   |
|---|-------------------|-------------------|---------------------|---------------------|---------------------|---------------------|-------------------|
|   | Week 2<br>(N=504) | Week 6<br>(N=523) | Week 12<br>(N=1873) | Month 6<br>(N=1420) | Month 12<br>(N=479) | Month 15<br>(N=112) | Final<br>(N=3753) |
| <b>Mean Change from Baseline – mmHg</b> |                   |                   |                     |                     |                     |                     |                   |
| Systolic BP                             | -1.2              | -0.0              | -1.1                | 0.1                 | 0.7                 | 0.9                 | -0.6              |
| Diastolic BP                            | -0.6              | 0.2               | -0.4                | -0.6                | -0.4                | 0.1                 | -0.6              |

*6.3.10.3.6 Studies to Assess Renal Effect of Celecoxib*

To evaluate the effects of celecoxib on renal function, three clinical pharmacology studies (Studies 010, 033 and 036) were conducted in selected groups of subjects and patients who have been identified at risk for adverse renal hemodynamic effects or excretory changes related to use of NSAIDs. A principal outcome measure in these studies was glomerular filtration rate (GFR, determined using Glofil®, sinistrine or inulin).

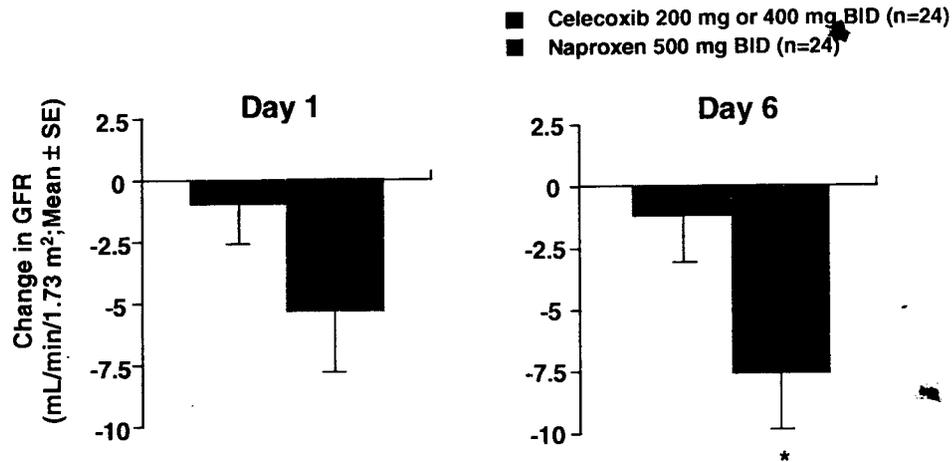
**Renal Effects in Healthy Elderly Subjects: Study 010**

In a single-center, in-patient, single-blind, randomized, crossover study, healthy elderly subjects (65 to 85 years of age) received either celecoxib 200 mg BID for five days followed by celecoxib 400 mg BID for the next five days, or they received naproxen 500 mg BID for 10 days. After taking one of these treatments and undergoing a seven-day washout period, subjects were crossed over to the other treatment regimen.

As depicted in Figure 30, GFR was unchanged from baseline ( $80.1 \pm 2.6$  mL/min/1.73m<sup>2</sup>) with celecoxib 200 mg BID on Day 1 and following escalation to 400 mg BID on Day 6. In contrast, GFR was reduced by 6% on Day 1 and 9% on Day 6 with naproxen 500 mg BID from a baseline value of  $84.3 \pm 2.9$  mL/min/1.73m<sup>2</sup>. A statistically significant reduction in GFR with naproxen 500 mg BID was detected on Day 6 when compared to the effect of celecoxib 400 mg BID. Five subjects exhibited 20% or greater reductions in GFR during naproxen 500 mg BID administration on either Day 1 or Day 6 as compared to Baseline. None of the subjects were observed to have 20% or greater reductions in GFR with either celecoxib 200 mg BID or celecoxib 400 mg BID.

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**Figure 30. Glomerular Filtration Rate - Effect of Celecoxib vs Naproxen: Study 010**



\* Significantly different from naproxen; p < 0.05.

Celecoxib and naproxen were associated with generally similar effects on urinary sodium excretion in terms of both the magnitude of the observed changes and the temporal pattern (Table 84). The significance of these observations is unclear since dietary sodium intake was not controlled in this study.

**Table 84. Sodium Excretion Responses to Celecoxib in Healthy Elderly Subjects: Study 010**

| Treatment | Base-line   | Treatment Period Day (Mean Change ± SE from Baseline) |              |             |            |            |             |              |           |             |
|-----------|-------------|---|--------------|-------------|------------|------------|-------------|--------------|-----------|-------------|
|           |             | 1   | 2            | 3           | 4          | 5          | 6           | 7            | 8         | 9           |
| Celecoxib | 137<br>± 10 | -41<br>± 10*  | -29<br>± 13* | -12<br>± 10 | -14<br>± 9 | -6<br>± 11 | -19<br>± 10 | -26<br>± 10* | -1<br>± 8 | -13<br>± 8† |
| Naproxen  | 127<br>± 7  | -49<br>± 7*   | -14<br>± 8   | 1<br>± 8    | 2<br>± 7   | 21<br>± 8  | -2<br>± 9   | -2<br>± 8    | 0<br>± 7  | 14<br>± 9   |

\* Significantly different from Baseline; p ≤ 0.05.

† Significantly different from naproxen; p ≤ 0.05.

**Renal Effects in Patients with Chronic Renal Insufficiency: Study 036**

In a multi-center, double-blind, randomized, placebo-controlled study, 71 patients with stable chronic renal insufficiency received either celecoxib 200 mg BID, naproxen 500 mg BID or placebo for seven days. Renal insufficiency was defined as a diminished GFR of 40 to 60 mL/min/ 1.73m<sup>2</sup> and an elevated but stable serum creatinine level (1.3-3.0 mg/dL) with no change in this value >1 mg/dL in the previous six months.

GFR was unchanged with celecoxib 200 mg BID when compared to naproxen 500 mg BID treatment or to placebo treatment (Table 85). Similarly no significant treatment effects were observed with naproxen 500 mg BID compared to placebo treatment. On Day 7, there was a trend for GFR to decline with time in all treatment groups including placebo and a statistically significant decrease was evident at the 1-2 hour timepoint for naproxen and the 2-3 hour postdose timepoint for celecoxib. Fractional sodium excretion with celecoxib 200 mg BID or naproxen 500 mg BID treatment was unchanged when compared to placebo treatment and no differences between celecoxib 200 mg BID and naproxen 500 mg BID treatment were evident. However, within-treatment group comparisons showed that fractional sodium excretion was significantly reduced with celecoxib 200 mg BID and naproxen 500 mg BID at most time points postdose on Day 1 from predose values. No treatment-related effects were evident on Day 7. Plasma renin activity (PRA) was not affected by celecoxib 200 mg BID or naproxen 500 mg BID treatment when compared to placebo treatment on Day 1 or on Day 7.

**Table 85. GFR and Fractional Sodium Excretion in Patients with Chronic Renal Insufficiency: Study 036**

| Assessment(a)                      | GFR (mL/min/1.73m <sup>2</sup> ) |                             |                            | Fractional Sodium Excretion (%) |                             |                            |
|------------------------------------|----------------------------------|-----------------------------|----------------------------|---------------------------------|-----------------------------|----------------------------|
|                                    | Placebo (N=19)                   | Celecoxib 200 mg BID (N=19) | Naproxen 500 mg BID (N=22) | Placebo (N=19)                  | Celecoxib 200 mg BID (N=19) | Naproxen 500 mg BID (N=22) |
| Day 1                              |                                  |                             |                            |                                 |                             |                            |
| Pre-dose                           | 31.8 ± 2.0                       | 31.5 ± 3.7                  | 36.9 ± 2.6                 | 2.6 ± 0.7                       | 2.9 ± 0.6                   | 3.4 ± 1.0                  |
| Postdose<br>(Change from Baseline) |                                  |                             |                            |                                 |                             |                            |
| 0-1 hr                             | 2.3 ± 2.6                        | 2.6 ± 2.7                   | -1.5 ± 2.7                 | -0.5 ± 0.4                      | -0.9 ± 0.4*                 | -0.6 ± 0.2*                |
| 1-2 hr                             | 1.7 ± 2.5                        | -2.2 ± 2.2                  | -3.9 ± 2.1                 | -0.8 ± 0.6                      | -1.0 ± 0.5*                 | -1.5 ± 0.4*                |
| 2-3 hr                             | -1.8 ± 2.0                       | -1.7 ± 2.7                  | -0.5 ± 2.5                 | -0.9 ± 0.7                      | -1.2 ± 0.4*                 | -1.9 ± 0.6*                |
| Day 7                              |                                  |                             |                            |                                 |                             |                            |
| Pre-dose                           | 34.4 ± 3.7                       | 35.4 ± 3.2                  | 37.1 ± 3.4                 | 2.1 ± 0.5                       | 3.6 ± 0.8                   | 3.4 ± 0.9                  |
| Postdose<br>(Change from Baseline) |                                  |                             |                            |                                 |                             |                            |
| 0-1 hr                             | -2.1 ± 3.0                       | -4.0 ± 2.6                  | -5.3 ± 3.1                 | -0.3 ± 0.5                      | 0.1 ± 0.5                   | 0.6 ± 0.4                  |
| 1-2 hr                             | -3.2 ± 3.1                       | -4.2 ± 3.7                  | -6.7 ± 2.7*                | -0.3 ± 0.5                      | 0.1 ± 0.8                   | 0.3 ± 0.6                  |
| 2-3 hr                             | -1.2 ± 3.9                       | -5.1 ± 2.4*                 | -4.2 ± 3.4                 | -0.5 ± 0.5                      | -1.0 ± 0.6                  | -0.5 ± 0.6                 |

Values are expressed as mean ± SE

\* Significantly different from the pre-dose level within treatment group; p ≤ 0.05.

(a) If GFR could not be calculated or exceeded 175 ml/min/1.73m<sup>2</sup>, the patient was excluded from the modified ITT cohort.

#### Renal Effects in Sodium-Depleted Young Healthy Subjects: Study 033

Study 033 was a single-center, double-blind, randomized, placebo-controlled, outpatient study comparing the renal effects of celecoxib to naproxen in sodium-depleted subjects.

Forty-one healthy young male subjects received celecoxib 200 mg BID, celecoxib 400 mg BID, naproxen 500 mg BID or placebo for seven days. Lack of adequate stimulation of the renin-angiotensin system in this study limited the activation of renal prostaglandin synthesis as a counterregulatory mechanism and resulted in the apparent inability to detect prostaglandin-mediated effects on renal function with dosing of naproxen. Additionally, large within-subject variability for GFR determinations obscured any treatment-related effects that may have taken place and precluded any meaningful analysis.

#### *6.3.10.3.7 Summary and Conclusions*

The incidence of renal adverse events with celecoxib was low and only marginally greater than placebo although this difference did achieve statistical significance. The most common adverse event that occurred with celecoxib treatment was peripheral edema. The incidence of peripheral edema and all other renal adverse events with celecoxib was similar to NSAIDs. Peripheral edema in celecoxib-treated patients was not associated with significant increases in body weight or blood pressure. Celecoxib was not associated with measurable changes in GFR in subgroups that are considered to be susceptible to the renal hemodynamic effects of NSAIDs. However, transient reductions in urinary sodium excretion were evident with celecoxib. The magnitude of this acute antinatriuretic effect was similar to that observed with NSAIDs. The clinical significance of the observations described above are uncertain and the evidence is inconclusive to determine whether celecoxib offers any renal safety benefit when compared to NSAID therapy. The available evidence suggests that the renal effects of celecoxib may be similar to NSAIDs.

#### *6.3.10.4 Hematologic Effects*

##### *6.3.10.4.1 Adverse Events*

Table 86 shows the incidences of adverse events relevant to bleeding, hemorrhagic or clotting abnormalities in the North American Controlled Arthritis Trials that occurred with incidence of 0.5% or greater in any treatment group. For celecoxib, the overall incidence of any adverse event related to bleeding varied from 1.3% to 2.3%. Although the highest overall celecoxib incidence occurred for the 400 mg BID dosage, there was no apparent dose-response effect. The incidence for NSAIDs was the highest at 3.8%, mostly resulting from the incidences of anemia and ecchymosis.

**Table 86. Bleeding-Related Adverse Events as Determined by the Investigator with an Incidence  $\geq 0.5\%$  in Any Treatment Group: North American Controlled Arthritis Trials**

| Adverse Event      | Placebo | Celecoxib |            |           |            |            | NSAID |
|--------------------|---------|-----------|------------|-----------|------------|------------|-------|
|                    |         | 50 mg BID | 100 mg BID | 200 mg QD | 200 mg BID | 400 mg BID |       |
| No. treated        | 1864    | 690       | 1779       | 453       | 1914       | 615        | 2098  |
| Any bleeding event | 1.6     | 2.2       | 1.6        | 1.3       | 2.2        | 2.3        | 3.8   |
| Vaginal hemorrhage | <0.1    | 0.2       | <0.1       | 0.7       | 0.0        | 0.2        | 0.1   |
| Anemia             | 0.4     | 0.6       | 0.3        | 0.4       | 0.7        | 0.8        | 1.6   |
| Ecchymosis         | 0.3     | 0.6       | 0.2        | 0.2       | 0.6        | 0.5        | 1.0   |

All numbers are percentages of patients unless otherwise specified.

Table 87 shows the statistical comparisons between recommended therapeutic doses of celecoxib and either placebo or NSAIDs for adverse events occurring in 0.5% or more of patients. No differences between celecoxib and placebo were statistically significant. However, the incidences of anemia, ecchymosis, and any bleeding-related event overall were statistically significantly higher for NSAIDs than for celecoxib.

**Table 87. Analysis of Bleeding-Related Adverse Events between Celecoxib and Placebo or NSAIDs**

| Adverse Event      | Celecoxib* | Placebo | p Value | Celecoxib* | NSAIDs | p Value |
|--------------------|------------|---------|---------|------------|--------|---------|
| No. treated        | 3512       | 1864    | -       | 2890       | 2098   | -       |
| Any bleeding event | 1.7        | 1.6     | -       | 1.9        | 3.8    | <0.001  |
| Vaginal Hemorrhage | 0.1        | <0.1    | -       | <0.1       | 0.1    | -       |
| Anemia             | 0.5        | 0.4     | -       | 0.5        | 1.6    | <0.001  |
| Ecchymosis         | 0.3        | 0.3     | -       | 0.4        | 1.0    | 0.015   |

Data are expressed in percentages of patients (except for p values).

#### 6.3.10.4.2 Adverse Events Causing Withdrawal

Six patients receiving NSAIDs withdrew due to anemia as compared with two patients receiving therapeutic doses of celecoxib and four patients overall. No placebo-treated patients withdrew for anemia. One celecoxib-treated patient and one NSAID-treated patient withdrew for ecchymosis.

#### 6.3.10.4.3 Serious Adverse Events

In the North American Controlled Arthritis Trials, no predominance of any single treatment group was suggested by analysis of serious adverse events possibly related to bleeding- or clotting-related disorders. The events analyzed were compiled from several body systems, including "platelet, bleeding and clotting disorders," "red blood cell

disorders,” and “vascular (extracardiac) disorders.” Four vascular (extracardiac) serious adverse events occurred in patients receiving celecoxib (0.4 events/100 patient-years), in four patients receiving NSAIDs (0.7 events/100 patient-years), and in two patients receiving placebo (1.0 events/100 patient-years). In addition, two patients, one taking celecoxib and the other taking an NSAID had a serious adverse event related to anemia. Finally, pulmonary embolism occurred in three NSAID-treated patients and one patient receiving celecoxib.

In the North American Long-term Open Label Arthritis Study, no single celecoxib dose level group predominated, indicating the absence of a dose response effect in the incidence of serious adverse events. Nineteen serious adverse events related to extracardiac vascular disorders occurred in patients in the North American Long-term Open Label Arthritis Study resulting in an incidence of 0.7 events per 100 patient-years of exposure.

#### *6.3.10.4.4 Clinical Laboratory Results*

Incidences of changes in clinical laboratory values in the North American 12-Week Placebo- and Active-Controlled Arthritis Trials were analyzed to assess the rate of clinically significant hematologic dysfunction (Table 88).

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**Table 88. Incidence of Hematologic Laboratory Changes: North American 12-Week Placebo- and Active-Controlled Arthritis Trials**

| Parameter                                | Celecoxib<br>100 and 200 mg BID |     | Placebo               |     | Naproxen<br>500 mg BID |      |
|--|---------------------------------|-----|-----------------------|-----|------------------------|------|
|  | No. of<br>Patients(a)           | %   | No. of<br>Patients(a) | %   | No. of<br>Patients(a)  | %    |
| Hemoglobin<br><10 g/dL                   | 2088                            | 0.4 | 1009                  | 0.3 | 1007                   | 0.5  |
| <6 g/dL or >3 g/dL<br>decrease           |                                 | 0.1 |                       | 0.1 |                        | 0.3  |
| Hematocrit<br><0.30                      | 2146                            | 0.1 | 1045                  | 0.3 | 1039                   | 0.19 |
| <0.25 or >0.10<br>decrease               |                                 | 0.1 |                       | 0   |                        | 0.19 |
| RBC<br><4.0 x 10 <sup>12</sup> /L        | 1990                            | 7.8 | 978                   | 4.8 | 978                    | 10.8 |
| <3.0 x 10 <sup>12</sup> /L               |                                 | 0   |                       | 0   |                        | 0    |
| WBC<br><4.0 x 10 <sup>12</sup> /L        | 2052                            | 4.9 | 1009                  | 3.9 | 1014                   | 3.3  |
| <2.0 x 10 <sup>12</sup> /L               |                                 | 0.1 |                       | 0   |                        | 0    |
| Platelets<br><100 x 10 <sup>9</sup> /L   | 2117                            | 0.1 | 1044                  | 0.1 | 1043                   | 0.1  |
| <25 x 10 <sup>9</sup> /L                 |                                 | 0   |                       | 0   |                        | 0    |
| Eosinophils<br>>0.7 x 10 <sup>9</sup> /L | 2176                            | 0.3 | 1066                  | 0.4 | 1061                   | 0.4  |
| >0.99 x 10 <sup>9</sup> /L               |                                 | 0.1 |                       | 0.1 |                        | 0.3  |
| Neutrophils<br><1.0 x 10 <sup>9</sup> /L | 2157                            | 0.1 | 1068                  | 0.1 | 1062                   | 0    |
| <0.5 x 10 <sup>9</sup> /L                |                                 | 0   |                       | 0.1 |                        | 0    |
| PT<br>>18 sec                            | 2034                            | 0.7 | 1000                  | 0.4 | 993                    | 0.8  |
| >36 sec                                  |                                 | 0.1 |                       | 0.2 |                        | 0.1  |
| PTT<br>>40 sec                           | 1944                            | 4.1 | 967                   | 4.1 | 957                    | 3.6  |
| >59 sec                                  |                                 | 0.9 |                       | 0.5 |                        | 0.7  |

a) No. of patients with normal values at Baseline

*6.3.10.4.5 Summary and Conclusions*

Celecoxib has no clinically important hematologic effects as assessed by adverse events and clinical laboratory parameters.

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## **7.0 BENEFIT/RISK RELATIONSHIP**

### **7.1 Summary of the Benefits of Celecoxib**

- Celecoxib is efficacious in the treatment of the signs and symptoms of OA, RA and in the management of pain.
- Celecoxib has been well tolerated by all populations studied, which are representative of the intended patient population. There is no evidence of dose-related increases in the incidence or type of adverse events. Over 500 arthritis patients have been treated with 2-4 times the full therapeutic dose for more than 3 months.
- The incidence of gastroduodenal ulcers that occurred with celecoxib both at therapeutic doses and 2-4 times the therapeutic dose, was significantly less than with NSAIDs and similar to placebo.
- The annual incidence of clinically significant UGI complications with celecoxib was only 0.20%. This incidence was significantly less than the 1.68% observed with NSAIDs and similar to that of placebo.
- Celecoxib did not affect platelet function at doses up to 12 times higher than the therapeutic dose.
- Celecoxib does not have clinically important interactions with other drugs including methotrexate, warfarin, lithium, glyburide, tolbutamide, or phenytoin.

### **7.2 Summary of Risks of Celecoxib**

- The novel COX-2 selective mechanism of action of celecoxib may result in unexpected toxicities.
- No prospective studies have been conducted in patients with advanced renal disease, congestive heart failure or liver dysfunction.
- The incidence of UGI complications with celecoxib (0.20%) was too low to identify patient populations at risk. UGI complications may occur in patients on celecoxib who have independent causal factors for the development of ulcer such as concurrent use of aspirin or *H. pylori* infection.
- The pharmacological activity of celecoxib to reduce pain and inflammation may mask and diminish the utility of these diagnostic signs in detecting infections.
- Celecoxib may be associated with reactions or exacerbations in patients with a history of sulfa allergy or NSAID-induced hypersensitivity reactions.

- Celecoxib has not been evaluated in patients with the aspirin triad (nasal polyps, rhinitis and asthma), or in patients who exhibit hypersensitivity reactions after taking aspirin or NSAIDs.
- Studies of celecoxib excretion in human milk have not been conducted but celecoxib has been shown to be excreted in rat milk.
- The effects of celecoxib on growth and development in pediatric patients are not known.

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## **8.0 CONCLUSIONS OF THE CELECOXIB CLINICAL PROGRAM**

Based on the results of clinical trials, it is concluded that celecoxib is efficacious in the treatment of the signs and symptoms of OA and RA and in the management of pain. The recommended therapeutic dose for OA is 200 mg per day administered as a single dose or as divided doses and the recommended therapeutic dose for RA is 100 mg or 200 mg BID. For alleviating acute pain, doses of 100 mg or 200 mg administered as needed every 4-6 hours up to a maximum daily dose of 400 mg are therapeutic.

Celecoxib has a wide therapeutic index and does not have the UGI toxicity or inhibitory platelet effects associated with COX-1 inhibition. The incidence of gastroduodenal ulceration and clinically significant UGI events in celecoxib treated patients at 2-4 times the full therapeutic dose was similar to placebo and significantly lower than with NSAIDs. At 6-12 times the therapeutic dose, celecoxib had no effect on platelet function.

Overall, celecoxib was well tolerated. GI symptoms (dyspepsia, nausea, abdominal pain) were more common in patients receiving celecoxib than in patients on placebo but significantly less than in patients receiving NSAIDs. Renal-related adverse events such as peripheral edema, were uncommon but more frequent than with placebo and similar to NSAIDs. Celecoxib had no apparent effects on vital signs and no adverse hematologic or hepatic effects.

As a specific COX-2 inhibitor, celecoxib has anti-inflammatory and analgesic properties without many of the mechanism-based, potentially serious adverse effects of non-selective COX inhibitors, NSAIDs. As such, this novel compound is an important contribution to the medical armamentarium for treating arthritis and pain.

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## 9.0 REFERENCES

1. Gierse, J.K.; Hauser, S.D.; Creely, D.P., et al. Expression and selective inhibition of the constitutive and inducible forms of human cyclo-oxygenase. *Biochem J* 305(1995):479-484.
2. Geis, G.S.; Stead, H.; Wallemark, C-B.; and Nicholson, P.A. Prevalence of mucosal lesions in the stomach and duodenum due to chronic use of NSAID in patients with rheumatoid arthritis or osteoarthritis, an interim report on prevention by misoprostol of diclofenac associated lesions. *J Rheumatol* 18(Suppl 28)(1991):11-14.
3. Schafer, A.I. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. *J Clin Pharmacol* 35(1995):209-219.
4. Palmer, B.F. Renal complications associated with use of nonsteroidal anti-inflammatory agents. *J Invest Med* 43(6)(1995):516-533.
5. Abramson, S.R., Weissman, G. The mechanisms of action of nonsteroidal anti-inflammatory drugs. *Arthritis Rheum* 32(1989):1-9.
6. Smith, W.L.; and DeWitt, D.L. Prostaglandin endoperoxide H synthases -1 and -2. *Adv Immunol* 62(1996):167-215.
7. Kargman, S.; Charleson, S.; Cartwright, M., et al. Characterization of prostaglandin G/H synthase 1 and 2 in rat, dog, monkey, and human gastrointestinal tracts. *Gastroenterology* 111(2)(1996):445-454.
8. Xie, W.; Chipman, J.G.; Robertson, D.L.; Erikson, R.L.; and Simmons, D.L. Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. *Proc Natl Acad Sci USA* 88(1991):2692-2696.

9. Kujubu, D.A.; Fletcher, B.S.; Varnum, B.C.; Lim, R.W.; and Herschman HR. TIS10, a phorbol ester tumor promoter-inducible mRNA from Swiss 3T3 cells, encodes a novel prostaglandin synthase/cyclooxygenase homologue. *J Biol Chem* 266(1991):12866-12872.
10. Penning, T.D.; Talley, J.J.; Bertenshaw, S.R., et al. Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (SC-58635, celecoxib). *J Med Chem* 40(9)(1997):1347-1365.
11. Masferrer, J.L.; Zweifel, B.S.; Seibert, K.; and Needleman, P. Selective regulation of cellular cyclooxygenase by dexamethasone and endotoxin in mice. *J Clin Invest* 86(1990):1375-1379.
12. Khan, K.N.M.; Venturini, C.M.; Bunch, R.T., et al. Interspecies differences in renal localization of cyclooxygenase isoforms: implications in nonsteroidal anti-inflammatory drug-related nephrotoxicity. *Toxicol Pathol* 26(5)(1998):612-620.
13. Anderson, G.D.; Hauser, S.D.; McGarity, K.L.; Bremer, M.E.; Isakson, P.C.; and Gregory, S.A. Selective inhibition of cyclooxygenase (COX)-2 reverses inflammation and expression of COX-2 and interleukin 6 in rat adjuvant arthritis. *J Clin Invest* 97(11)(1996):2672-2679.
14. Elliott, G.A.; Purmalis, A.; VanderMeer, D.A.; and Denlinger, R.H. The propionic acids. Gastrointestinal toxicity in various species. *Toxicol Pathol* 16(2)(1988):245-250.
15. Langley, G.B., and Sheppard, H. Problems associated with pain measurement in arthritis: comparison of visual analogue and verbal rating scales. *Clin Exp Rheumatol* 2(1984):231-234.

16. The Cooperating Clinics Committee of the American Rheumatism Association. A seven day variability study of 499 patients with peripheral rheumatoid arthritis. *Arthritis Rheum* 8(1965):302-334.
17. Bellamy, N.; Buchanan, W.W.; Goldsmith, C.H.; Campbell, J., and Stitt, L.W. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients osteoarthritis of the hip or knee. *J Rheumatol* 15(1988):1833-1840.
18. Altman, R.; Asch, E.; Bloch, G, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis Rheum* 29(1986):1039-1049.
19. Lequesne, M.G.; Mery, C.; Samson, M., and Gerard, P. Indexes of severity for osteoarthritis of the hip and knee: Validation - value in comparison with other assessment tests. *Scand J Rheumatol Suppl* 65(1987):85-89.
20. American Pain Society Quality of Care Committee. Quality improvement guidelines for the treatment of acute pain and cancer pain. *JAMA* 274(1995):1874-1880.
21. Ware, J.E. SF-36 Health Survey, Manual, and Interpretation Guide. Boston: The Health Institute, New England Medical Center, 1993.
22. Felson, D.T.; Anderson, J.J.; Boers, M., et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 38(1995):727-735.
23. Wolfe, F.; Kleinheksel, S.M.; Cathey, M.A.; Hawley, D.J.; Spitz, P.W., and Fries, J.F.. The clinical value of the Stanford health assessment questionnaire functional disability index in patients with rheumatoid arthritis. *J Rheumatol* 15(1988):1480-1488.

24. Presentation of efficacy results of single-dose analgesics for studies using acute pain models. FDA, Draft Doc., January 1997.
25. Bocanegra, T.S.; Weaver, A.L.; Tindall, E.A., et al. Diclofenac/misoprostol compared with diclofenac in the treatment of osteoarthritis of the knee or hip: a randomized, placebo-controlled trial. *J Rheumatol* 25(1998):1602-1611.
26. Silverstein, F.E.; Graham, D.Y.; Senior, J.R.; Davies, H.W.; Struthers, B.J.; Bittman, R.M.; and Geis, G.S. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 123(1995):241-249.

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