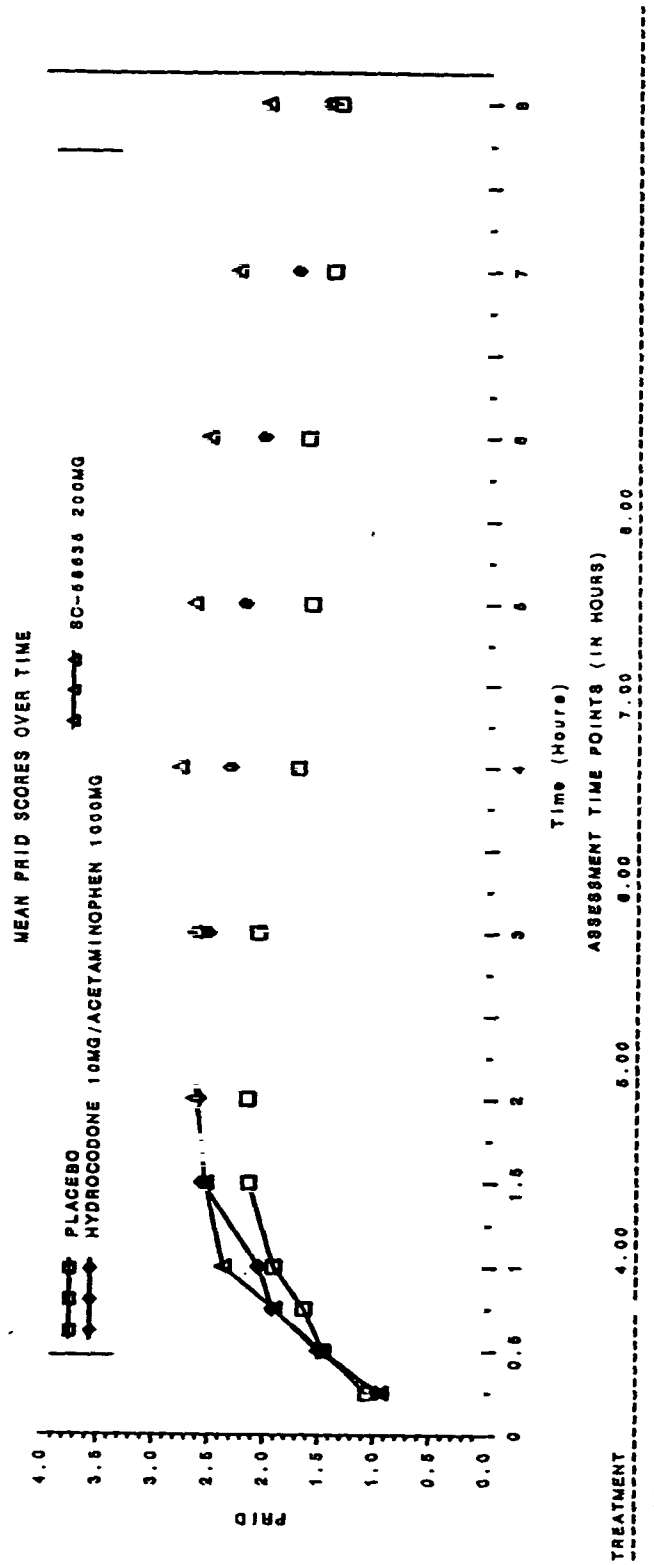
Figure 73:Plot of PRID scores for hours 0-8




ASSESSMENT TIME POINTS (IN HOURS)

| TREATMENT | 4.00 | 5.00 | 6.00 | 7.00 | 8.00 |
|---|---|---|---|---|---|
| HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG | 2.32 ( 2.10) 44(a) AB(a) | 2.20 ( 2.07) 40 AB | 2.03 ( 2.05) 38 A | 1.72 ( 1.92) 34 A | 1.44 ( 1.77) 31 A |
| SC-58636 200MG | 2.76 ( 2.37) 47 A | 2.66 ( 2.36) 42 A | 2.59 ( 2.36) 40 A | 2.27 ( 2.27) 36 A | 2.00 ( 2.24) 33 A |
| PLACEBO | 1.71 ( 2.22) 28 B | 1.59 ( 2.18) 25 B | 1.88 ( 2.22) 27 A | 1.40 ( 1.87) 24 A | 1.34 ( 1.68) 24 A |
| TREATMENT P-VALUE (b) | 0.0329 | 0.0330 | 0.0375 | 0.052 | 0.187 |
| TRT*BASELINE P-VALUE (c) | 0.7729 | 0.8228 | 0.8004 | 0.6820 | 0.4866 |
| TRT*CENTER P-VALUE (d) | 0.6224 | 0.6946 | 0.4913 | 0.3265 | 0.2869 |
| GENDER P-VALUE (b) | 0.0244 | 0.0146 | 0.7107 | 0.2216 | 0.3116 |
| BASELINE P-VALUE (b) | 0.0156 | 0.0067 | 0.0046 | 0.0003 | 0.0172 |
| CENTER P-VALUE (b) | 0.1149 | 0.0007 | 0.0005 | 0.0003 | 0.0007 |
| SURGERY TYPE P-VALUE (d) | 0.1177 | 0.2118 | 0.3364 | 0.4423 | 0.4487 |
| RMS ERROR (b) | 2.1177 | 2.1118 | 2.1110 | 1.9777 | 1.8939 |

(a) Sample size is not extrapolated.
(b) Model: PRID = mu + Ti + pp(0) + interaction term + center + error.
(c) Based on model (b) Lsmeans. Treatments with the same
letter are not significantly different from each other.
(d) Model: PRID = mu + Ti + Pi(0)] + center + error.
Model: PRID = mu + Ti + Pi(0)] + center term + effect term +
center + error.

Comparing celecoxib and hydrocodone the differences were not significant at any time points.

The time to rescue for celecoxib was significantly different compared to placebo ($p<.05$) (figure 74). For hydrocodone the difference was not significant. There was no significant difference between celecoxib and hydrocodone.

**Figure 74: Time to rescue medication**

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| TREATMENT | N | PATIENTS WHO TOOK RESCUE MEDICATION N (%) | MEDIAN TIME IN N : MIN (a,b) | 95%-CI IN H : MIN (c) |
|---|---|---|---|---|
| HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG | 71 | 39 ( 54%) | 06:48 (AB ) | 05:11 TO >08:00 |
| SC-58635 200MG | 73 | 31 ( 42%) | >08:00 (B ) | 05:20 TO >08:00 |
| PLACEBO | 70 | 44 ( 63%) | 04:00 (B ) | 02:23 TO 04:04 |

[BY KAPLAN-MEIER ESTIMATE (SEE MILLER, SURVIVAL ANALYSIS, PAGE 75)]
(b) Logrank test applied as in Fisher's Protected LSD. Treatments with the same letter are not significantly different from each other.
(c) Method of Gibon & Lee, Cancer Treat Rep, 1983.

The time to onset of perceptible pain relief for celecoxib and hydrocodone was not different from placebo (figure 75).

**Figure 75: Time to onset of perceptible pain relief**

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Time to Onset of Perceptible Pain Relief (Hours)

| TREATMENT | N | PATIENTS WITH PERCEPTIBLE PR N (%) | MEDIAN TIME IN H : MIN (a,b) | 95%-CI IN H : MIN (c) |
|---|---|---|---|---|
| HYDROCODONE 10MG/ ACETAMINOPHEN 1000MG | 71 | 61 ( 86%) | 00:21 ( A ) | 00:15 TO 00:30 |
| SC-58635 200MG | 73 | 60 ( 82%) | 00:18 ( A ) | 00:17 TO 00:36 |
| PLACEBO | 70 | 55 ( 79%) | 00:29 ( A ) | 00:19 TO 00:43 |

[BY KAPLAN-MEIER ESTIMATE (SEE MILLER, SURVIVAL ANALYSIS, PAGE 75)]
(b) Logrank test applied as in Fisher's Protected LSD. Treatments with the same letter are not significantly different from each other.
(c) Method of Gibon & Lee, Cancer Treat Rep, 1983.

Secondary efficacy measures:

Mean PID (VAS) scores for celecoxib were significantly different from placebo at 4 and 5 hours only. For hydrocodone the differences were not significant at any

time points. The differences between celecoxib and hydrocodone were not significant.

The mean SPID, PPID, TOTPAR, SPRID, time first experienced at least 50% pain relief, time to onset of meaningful pain relief for celecoxib compared to placebo was not significantly different. The same was true for hydrocodone.

For the proportion of patients experiencing at least 50% pain relief the differences were significant only at 5 hours for both celecoxib and hydrocodone compared to placebo.

The differences in distribution of time to onset of analgesia was significantly different comparing celecoxib and placebo as well as hydrocodone and placebo ($p<.05$).

Efficacy measures for the MDAP:

For the variables of maximum pain intensity, pain relief, and patient's global evaluation the proportion of patients in each category were numerically similar across treatment groups.

Overall the number of patients withdrawing due to treatment failure was the same in the celecoxib and hydrocodone groups.

For the number of doses of study medication taken on days 2-5 the celecoxib group was generally significantly different (fewer doses) as compared to the hydrocodone group.

For time between 2 consecutive doses on days 2-5, and the mean maximum pain relief scores the differences between groups was not significant.

The mean maximum pain intensity scores were significantly different favoring the celecoxib treatment group.

For APS measures, the only significant difference was in response to the first question.

There were no significant differences for the patient global assessment between the 2 groups.

For pre-dose pain intensity days 2-5 the differences between the 2 groups was significant on days 3 and 4.

e. Reviewer's comments:

The primary endpoints for hydrocodone did not differ from placebo. For the single dose period, celecoxib was superior to placebo for time to rescue medication but not for time to onset of perceptible pain relief. In addition, for the time specific measures of efficacy celecoxib differed from placebo starting at 4 hours and was inconsistently superior to placebo over the remaining time out to 8 hours. *The fact that hydrocodone did not differ from placebo in the SDAP significantly limits the ability to analyze the MDAP assessment since no placebo is present and celecoxib is compared only to hydrocodone.* Nevertheless if celecoxib was shown to be significantly superior to hydrocodone during this time, it might then have been possible to conclude that celecoxib was effective in the MDAP. However, this was not the case. For most measures, celecoxib was not significantly superior to hydrocodone for the MDAP. Therefore, this study failed to demonstrate that in terms of efficacy, celecoxib was superior to placebo in the single dose period or superior to hydrocodone in the multiple dose period.

Taken together with study 085, celecoxib does not appear to be efficacious for acute pain in this model. The sponsor has pooled studies 085 and 086 for analysis in the ISE and this will be further discussed in the section on the integrated summary of efficacy below.

8. Trial 074

Multi-center double blind placebo controlled comparison of the analgesic effect of celecoxib 200 mg bid, diclofenac 75 mg SR bid, and placebo in patients who have undergone hernia repair surgery.

a. Objectives and rationale

The primary objective of this study was to compare the analgesic effect of celecoxib (200 mg bid) versus placebo for the first 24 hours post-operatively in patients following hernia repair surgery.

The secondary objectives of the study were to: 1) compare the analgesic effect of celecoxib versus placebo for the first 3 days post-operatively in patients following hernia repair surgery; 2) compare the analgesic effect of diclofenac (75 mg SR bid)versus placebo in patients following hernia repair surgery; 3) compare the analgesic effect of celecoxib versus diclofenac in patients following hernia repair surgery; 4) compare the total amount of rescue medication administered to patients in the celecoxib treatment group compared to patients in the placebo and diclofenac treatment groups; 5) evaluate the safety of celecoxib in patients following hernia repair surgery.

b. Design

The trial was a multi-center double blind (double dummy) randomized active and placebo controlled parallel group comparison of the safety and analgesic effects

of celecoxib 200 mg bid and diclofenac 75 mg SR bid compared to placebo orally administered to patients following hernia repair surgery. Patients who met entry criteria for the study were randomized to receive either celecoxib, diclofenac, or placebo in a 2:2:1 ratio respectively. Pain was assessed by each patient on the day of surgery immediately prior to the first dosing at 1-2 hours post surgery and every 2 hours for the first 24 hours following administration of the first dose of medication. Patients were further assessed on days 2-4.

c. Protocol

1 Population

To qualify for the study participation candidates must have:

1. Been male or female and at least 18 years of age.
2. For women of childbearing potential, confirmed use of adequate contraception, not been lactating, and had a negative pregnancy test (urine) at screening, prior to surgery.
3. Satisfactory health as determined by the Investigator on the basis of medical history and physical examination. 4. Undergone primary, unilateral inguinal hernia-repair surgery performed either under local anesthesia or general plus local anesthesia.
5. Been scheduled to be discharged from the hospital within 24 hours after the end of surgery.
6. Provided written informed consent prior to undergoing any procedures for this study.

Candidates were not eligible for admission if they had any of the following:

1. Undergone a multiple or recurrent hernia-repair procedure.
2. Undergone emergency hernia-repair surgery of any type.
3. The surgical procedure was performed using spinal anesthesia.
4. The surgical procedure involved laparoscopy.
5. A history of uncontrolled chronic disease, that would, in the opinion of the Investigator, contraindicate study participation or confound interpretation of the results.
6. Any cognitive impairment that would, in the Investigator's opinion, preclude study participation or compliance with protocol-mandated procedures.
7. Active or suspected esophageal, gastric, pyloric channel, or duodenal ulceration or bleeding within 30 days prior to receiving the first dose of study medication.
8. Any known laboratory abnormality that would, in the opinion of the Investigator, contraindicate study participation, including aspartate transaminase (AST) or alanine transaminase (ALT) > 1.5, creatinine > 1.5, or urea > 1.5 times the upper limit of the reference range.
9. A history of known alcohol, analgesic, or narcotic abuse.
10. Known hypersensitivity to analgesics, NSAIDs, cyclooxygenase inhibitors, lactose, or sulfonamides.
11. Inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), a chronic or acute renal or hepatic disorder, a significant coagulation defect, or

any condition that would, in the Investigator's opinion, preclude the use of an NSAID (e.g. congestive cardiac failure).
12. A history of asthma or bronchospasm.
13. A history of intolerance to diclofenac or tramadol.
14. Active malignancy of any type, or a history of malignancy. (Patients with a history of basal cell carcinoma that had been successfully treated were acceptable. Patients with a history of other malignancies, surgically removed and with no evidence of recurrence for at least 5 years before enrollment in the study, were also acceptable)
15. Received any investigational medication within 30 days prior to the first dose of study medication or was scheduled to receive an investigational drug other than celecoxib during the course of this study.
16. Were previously admitted to this study.

2 Endpoints

All efficacy analyses were based on the ITT patient population. The primary measures of efficacy were: 1) AUC for pain intensity scores (categorical and VAS) observed within the 24 hour period following surgery; 2) time to first use of rescue medication and the amount used in the 24 hour period; 3) global evaluation of study medication at the end of day 1.

The secondary measures of efficacy were: 1) AUC for pain intensity scores (categorical and VAS) until the end of study day 4; 2) time to first use of rescue medication and the total amount used by the end of study day 4; 3) maximum pain intensity scores and global evaluation of study medication on study days 2-4.

Safety was evaluated based on exam, vital signs, laboratory values and adverse events.

3 Statistical considerations

The sample size calculation of 250 patients was based on the comparison between placebo and each active treatment for one primary efficacy variable. A sample size of 50 patients for the placebo and 100 patients for each treatment arm was chosen to detect a difference of at least .5 units with at least 80% power and an alpha level of .05 (two-sided test).

AUC and pain intensity were analyzed by ANCOVA model with treatment and center as factors and baseline pain values as covariates. Clinical data were compared using Kruskal Wallis test applied to change from Baseline to end of study. Shift tables and a Stuart Maxwell or McNemars test were used to determine significant distributional changes over the course of the study. Laboratory values were compared across treatment groups using Chi-square test. Changes from

baseline values within treatment groups were analyzed using a paired t-test and changes form baseline were also compared using a Kruskal Wallis test.

d. Results

1 Patient disposition

A total of 284 patients were enrolled into this study and randomized to receive one of three treatments: 112 patients received celecoxib, 114 received diclofenac, and 58 received placebo. A total of 262 patients completed the study and 22 withdrew from the study early. The treatment groups were comparable at baseline for age, race, gender, height, and weight. The treatment groups were comparable for surgical procedure and baseline pain intensity (categorical). However, 12-21% of patients reported a baseline pain intensity of none and 38-49% had mild pain intensity. Across treatment groups the baseline pain intensity (VAS) ranged from 28-31.

2 Efficacy endpoint outcomes

Analysis of primary endpoints:

Across treatment groups mean AUC 0-24 (categorical) were statistically significant ($p<.001$).Mean AUC 0-24 scores for celecoxib and diclofenac were statistically significant compared to placebo. The same was true for AUC 0-24 (VAS) (see Figure 76).



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# Figure 76: Area under the pain intensity curve

TABLE 8.1
AREA UNDER THE PAIN INTENSITY CURVE FROM PRIOR TO FIRST DOSE TO 24 HOURS POSTDOSE

INTENT-TO-TREAT (ITT) PATIENTS (a)

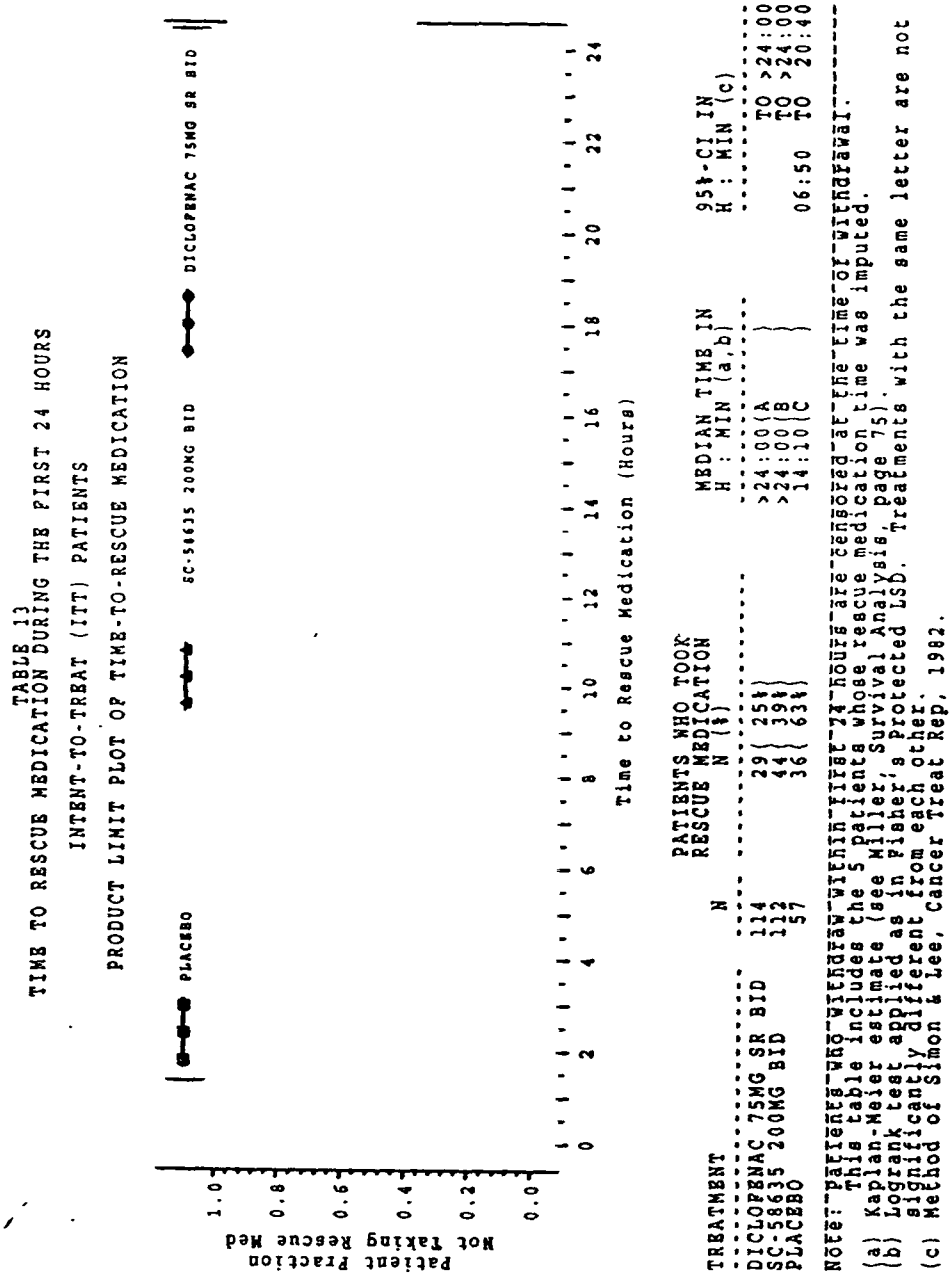
| | PLACEBO (N= 57) | SC-58635 200MG BID (N=112) | DICLOFENAC 75MG SR BID (N=114) | p-VALUE (b) |
|---|---|---|---|---|
| AUC(0-24 HOURS, CATEGORICAL) | | | | <0.001 |
| ALL PAIN INTENSITY ASSESSMENTS INCLUDED | | | | |
| N | 55 | 112 | 114 | |
| MEAN | 43.1 | 33.7 | 28.4 | |
| STD DEV | 17.08 | 19.41 | 18.98 | |
| MEDIAN | 43.8 | 31.7 | 24.9 | |
| RANGE | | | | |
| AUC(0-24 HOURS, VISUAL ANALOG SCALE) | | | | <0.001 |
| ALL PAIN INTENSITY ASSESSMENTS INCLUDED | | | | |
| N | 55 | 111 | 114 | |
| MEAN | 1017.1 | 826.0 | 611.9 | |
| STD DEV | 584.68 | 617.24 | 579.57 | |
| MEDIAN | 943.0 | 751.3 | 396.1 | |
| RANGE | | | | |

| p-VALUES FOR PAIRWISE COMPARISON (c) | SC-58635 VS. PLACEBO | DICLOFENAC VS. PLACEBO | SC-58635 VS. DICLOFENAC |
|---|---|---|---|
| AUC(0-24 HOURS, CATEGORICAL) | 0.001 | <0.001 | 0.057 |
| AUC(0-24 HOURS, VISUAL ANALOG SCALE) | 0.034 | <0.001 | 0.011 |

(a) This table is based on interpolated or LOCF data. AUC is a measure of average pain intensity.
(b) Two-way Analysis of Variance with treatment and center as factors.
(c) From contrast statement from Model (b).

For time to first rescue medication in the first 24 hour post dose period the times for celecoxib and diclofenac were statistically significant compared to placebo (figure 77).

**Figure 77: Time to rescue medication**




| TREATMENT | N | PATIENTS WHO TOOK RESCUE MEDICATION N (%) | MEDIAN TIME IN H : MIN (a,b) | 95%-CI IN H : MIN (c) |
|---|---|---|---|---|
| DICLOFENAC 75MG SR BID | 114 | 29 ( 25%) | >24:00 (A | TO >24:00 |
| SC-58635 200MG BID | 112 | 44 ( 39%) | >24:00 (B | TO >24:00 |
| PLACEBO | 57 | 36 ( 63%) | 14:10 (C | 06:50 TO 20:40 |

NOTE: Patients who withdraw within first 24 hours are censored at the time of withdrawal.

This table includes the 5 patients whose rescue medication time was imputed.

(a) Kaplan-Meier estimate (see Miller, Survival Analysis, page 75).

(b) Logrank test applied as in Fisher's Protected LSD. Treatments with the same letter are not significantly different from each other.

(c) Method of Simon & Lee, Cancer Treat Rep, 1982.

Across treatment groups the difference in the amount of rescue medication taken during the first 24 hours was statistically significant for celecoxib and diclofenac compared to placebo.

The mean global evaluation score for celecoxib was not significantly different from placebo (p=.231). However for diclofenac there was a significant difference (p=.046).

Analysis of secondary endpoints:

Mean AUC 0-12 pain intensity (categorical) for celecoxib and diclofenac showed a statistically significant difference from placebo. Mean AUC 0-72 pain intensity (categorical) for celecoxib and diclofenac showed a statistically significant difference from placebo.

Mean AUC 0-12 (VAS) for celecoxib was not significantly different from placebo while for diclofenac the difference was significant. Mean AUC 0-72 (VAS) for celecoxib and diclofenac showed a statistical difference from placebo.

There was no significant difference in the time to first use of rescue medication in the first 12 hours between celecoxib and placebo while for diclofenac the difference was significant. The difference in time to use of rescue medication 0-72 hours was significant between celecoxib and placebo. The same was true for diclofenac.

The differences in the amount of rescue medication used for the 0-24 hour, 0-48 hour and 0 to final interval was significant for celecoxib compared to placebo. The same was true for diclofenac.

The mean scores of pain intensity assessments on days 2-4 were significantly different favoring celecoxib over placebo.

The mean maximum pain intensity scores for celecoxib were significantly different from placebo on days 2-4 (but not day 1). The same was true for diclofenac.

The mean patient Global Evaluation scores for the celecoxib 200 mg BID treatment group were numerically higher than the placebo treatment group on all four study days. For the pair wise comparisons, these differences were statistically significant on study days 2 (p=0.003), 3 (p=0.005), and 4 (p=0.009).

e. Reviewer's comments

For all of the primary efficacy endpoints except global evaluation the celecoxib treatment group was significantly different from placebo. This was further

supported by the secondary endpoints. The sponsor however did not measure time to onset of analgesia by the stopwatch method. There was no presentation of time specific measures of efficacy such as PID etc. Measures on days 2-4 may support the efficacy of celecoxib in the multiple dose period. Based on the above the present study may be used as supportive of the analgesic efficacy of celecoxib. However, there are several concerns. Patients were able to take tramadol as oral rescue as needed during the study. This can confound the results. The study may also have been confounded by the variability of anesthesia technique, the low baseline pain intensity, and the concomitant use of drugs that are potential analgesic adjuvants. Patients were allowed to use either local anesthesia alone or local anesthesia plus general anesthesia. A wide range of local anesthesia was used, ranging from drugs with intermediate duration of action (60-120 minutes), such as lidocaine, to combinations of medications with a prolonged duration (>400-450 minutes), such as bupivacaine administered with mepivacaine and adrenaline. General anesthesia could have included pre-operative benzodiazepines, inhalational anesthesia, and opioid analgesia with a potentiating neuroleptic in addition to local anesthesia. These issues limit confidence in the results of this trial.

9. Trial 075

Multicenter double blind randomized placebo controlled study comparing the opioid sparing effect of celecoxib 200 mg bid, diclofenac 75 mg bid, and placebo in patients who have undergone routine hip replacement surgery.

a. Objectives and rationale

The primary objective of this study was to evaluate if celecoxib has a significant opioid sparing effect in patients following elective hip surgery compared to placebo. The secondary objectives of the study were to : 1) compare the opioid sparing effect of celecoxib versus diclofenac in patients following hip surgery; 2) compare the opioid sparing effect of celecoxib, diclofenac and placebo at 12, 24, and 36 hours post surgery; 3) compare with placebo the analgesic efficacy of celecoxib over the first 36 hours post-surgery and until the end of the study in patients following elective hip surgery; 4) evaluate the safety of celecoxib in patients following hip surgery.

b. Design

The study was a multi-center double blind randomized active and placebo controlled parallel group comparison of the opioid sparing effect of celecoxib 200 mg bid and diclofenac 75 mg SR bid compared to placebo orally administered to patients following elective hip replacement surgery. Patients who met all the entrance criteria were randomized to receive celecoxib, diclofenac, or placebo in addition to morphine which was available through PCA or as a bolus. Patients received the first dose of study medication 2-6 hours before surgery and then

through day 5. Patients with inadequate pain relief were allowed morphine and Tramadol prn.

c. Protocol

1 Population and procedures

Inclusion and Exclusion criteria:

To qualify for study participation, patients must have:

1. Been male or female 50 years of age and above.
2. For women of childbearing potential, confirmed use of adequate contraception, not been lactating, and had a negative pregnancy test (urine) at screening, prior to surgery.
3. Been in satisfactory health as determined by the Investigator on the basis of medical history and physical examination.
4. Undergone primary, unilateral hip replacement surgery performed under general anesthesia plus a single administration of local anesthesia into the wound.
5. Undergone a surgical procedure involving cement. This criterion was deleted in protocol amendment No. 1, dated 21 April 1998.
6. Post-operative analgesia with morphine, administered via PCA equipment.
7. Been scheduled to be hospitalized at least 4 days post-operatively.
8. Provided written informed consent prior to undergoing any procedures for this study.

Patients were not eligible for admission if they had any of the following:

1. Undergone a revision to a previous hip replacement procedure.
2. Undergone emergency hip replacement procedure.
3. A fracture of either hip.
4. A history of uncontrolled chronic disease, that would, in the opinion of the Investigator, contraindicate study participation or confound interpretation of the results.
5. Any cognitive impairment that would, in the Investigator's opinion, preclude study participation or compliance with protocol-mandated procedures.
6. Active or suspected esophageal, gastric, pyloric channel, or duodenal ulceration or bleeding within 30 days prior to receiving the first dose of study medication.
7. Any known laboratory abnormality that would, in the opinion of the Investigator, contraindicate study participation, including aspartate transaminase (AST) or alanine transaminase (ALT) > 1.5, creatinine > 1.5, or urea > 1.5 times the upper limit of the reference range.
8. A history of known alcohol, analgesic, or narcotic abuse.
9. Known hypersensitivity to analgesics, NSAIDs, cyclooxygenase inhibitors, lactose, or sulfonamides.
10. Inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), a chronic or acute renal or hepatic disorder, a significant coagulation defect, or any condition that would, in the Investigator's opinion, preclude the use of an NSAID (e.g. congestive cardiac failure).
11. A history of asthma or bronchospasm.

12. A history of intolerance to diclofenac, tramadol, or opioids.
13. Active malignancy of any type, or a history of malignancy. (Patients with a history of basal cell carcinoma that had been successfully treated were acceptable. Patients with a history of other malignancies, surgically removed and with no evidence of recurrence for at least 5 years before enrollment in the study, were also acceptable).
14. Received any investigational medication within 30 days prior to the first dose of study medication or was scheduled to receive an investigational drug other than celcoxib during the course of this study.
15. Were previously admitted to this study.

The randomization ratio was 2:2:1 (celecoxib:diclofenac:placebo). This was a double blind double dummy study. Pain assessments were made every 2 hours for the first 24 hours starting after surgery.

2 Endpoints

The primary measures of efficacy were: 1) the total amount of morphine used; 2) time to last dose of morphine for each patient.

The secondary measures of efficacy were: 1) cumulative use of morphine at 12, 24 and 36 hours post surgery; 2) cumulative use of tramadol at 12, 24, and 36 hours post surgery and the total amount used; 3) AUC of pain intensity scores over the first 36 hours post surgery and until the end of study; 4) maximum pain intensity scores and patients global evaluation of study medication on Study days 1-5.

3 Statistical considerations

A sample size of 50 patients in the placebo group and 100 patients in each active treatment group was chosen to detect a difference of at least .25 with at least 80% power and an alpha level of .05. Cochran-Mantel-Haenszel analyses were used for consumption of morphine, tramadol. AUC values were subjected to ANOVA with treatment group, age, sex, and center as factors. Other analyses are as described. There were a number of patients with protocol violations including use of prohibited medications in 22/56 placebo, 47/111in celecoxib groups and 59/116 in the diclofenac group. All patients were included in the ITT analysis.

d. Results

1 Patient disposition and comparability

A total of 283 patients were enrolled in the study and randomized to receive one of three treatments: 111 patients received celecoxib, 116 received diclofenac, and 56 received placebo. A total of 244 patients completed the study. The treatment groups were comparable for age, race, gender, height, weight, blood pressure and heart rate, mean duration of surgery, time to connection to PCA.

## 2 Efficacy endpoint outcomes

### Analysis of primary measures of efficacy:

The mean total morphine consumption for the celecoxib group was not significantly different from placebo (p=.129). For the diclofenac group the difference was significant (p<.001) (see Figure 78).

TABLE 8
TOTAL MORPHINE CONSUMPTION (INCLUDING BOLUS) AND DURATION OF PCA
ALL PATIENTS WHO TOOK AT LEAST ONE DOSE OF STUDY MEDICATION

| | PLACEBO (n= 56) | SC-58635 200mg BID (n=111) | DICLOFENAC 75mg SR BID (n=116) | p-VALUE |
|---|---|---|---|---|
| TOTAL MORPHINE CONSUMPTION (MG) | | | | |
| N | 56 | 111 | 116 | |
| MEAN | 43.9 | 36.9 | 27.2 | |
| STD DEV | 29.70 | 27.22 | 21.94 | |
| MEDIAN | 38.0 | 32.0 | 24.0 | |
| RANGE | 3 - 150 | 0 - 137 | 0 - 112 | |
| Up to 10mg | 8 ( 14%) | 17 ( 15%) | 31 ( 27%) | <0.001 |
| 11 to 20mg | 4 ( 7%) | 12 ( 11%) | 24 ( 21%) | |
| 21 to 30mg | 8 ( 14%) | 25 ( 23%) | 20 ( 17%) | |
| 31 to 40mg | 11 ( 20%) | 18 ( 16%) | 14 ( 12%) | |
| 41 to 50mg | 5 ( 9%) | 12 ( 11%) | 10 ( 9%) | |
| 51 to 100mg | 18 ( 32%) | 24 ( 22%) | 16 ( 14%) | |
| More than 100mg | 2 ( 4%) | 3 ( 3%) | 1 ( 1%) | |
| TOTAL | 56 (100%) | 111 (100%) | 116 (100%) | |
| DURATION OF PCA (HH:MM) | | | | |
| N | 53 | 106 | 112 | |
| MEAN | 38:02 | 35:20 | 27:28 | |
| STD DEV | 22:22 | 19:23 | 19:16 | |
| MEDIAN | 36:00 | 37:19 | 27:05 | |
| RANGE | 0:00 - 111:30 | 0:00 - 94:10 | 0:00 - 82:11 | |
| Up to 12 hours | 6 ( 11%) | 14 ( 13%) | 31 ( 28%) | <0.001 |
| 12 to 18 hours | 2 ( 4%) | 5 ( 5%) | 7 ( 6%) | |
| 18 to 24 hours | 5 ( 9%) | 15 ( 14%) | 15 ( 13%) | |
| 24 to 36 hours | 16 ( 30%) | 16 ( 15%) | 24 ( 21%) | |
| 36 to 48 hours | 15 ( 28%) | 28 ( 26%) | 20 ( 18%) | |
| More than 48 hours | 9 ( 17%) | 28 ( 26%) | 15 ( 13%) | |
| TOTAL | 53 (100%) | 106 (100%) | 112 (100%) | |
| p-VALUES FOR PAIRWISE COMPARISONS | PLACEBO VS SC-58635 | PLACEBO VS DICLOFENAC | SC-58635 VS DICLOFENAC | |
| TOTAL CONSUMPTION | 0.129 | <0.001 | 0.003 | |
| DURATION | 0.964 | 0.005 | <0.001 | |

p-values from Cochran-Mantel-Haenszel analyses stratified by center

**Figure 78: Total morphine consumption**

The difference in mean duration of PCA between celecoxib and placebo was not significant (p=.964). However, the difference for diclofenac was significant (p=.005).

Analysis of secondary measures of efficacy:

Cumulative morphine consumption of celecoxib was not different from placebo at 12, 24, and 36 hours.

However, the mean morphine consumption from 24-36 hours post-surgery for the celecoxib 200 mg BID treatment group (6.0 mg) was lower than the placebo treatment group (9.0 mg); this was a statistically significant difference (p=0.027). *It is not clear whether this statistical difference translates into any meaningful clinical effect.* For the diclofenac 75 mg SR BID treatment group (4.0 mg), the mean morphine consumption from 24-36 hours post-surgery was numerically lower than the placebo treatment group. This difference was also statistically significant (p<0.001).

Mean total tramadol consumption for the celecoxib group was not significantly different from placebo. The time to first dose of tramadol was not significantly different from placebo. Mean tramadol consumption at 12, 24 and 36 hours was not significantly different from placebo.

The mean pain intensity score (categorical) for the celecoxib group was significantly different from placebo (p=.022) at 0-36 hours. However there was no difference at the 0-120 hours time. For pain intensity assessments (VAS) the difference between celecoxib and placebo was significant at the 0-36 hour assessment but not at the 0-120 hour assessment.

The mean maximum pain intensity score for celecoxib was not significantly different from placebo.

The mean global evaluation scores for celecoxib were not different from placebo except on day 3 (p=.017).

e. Reviewer's comments and conclusions

This study fails to demonstrate that celecoxib is effective in the management of acute pain in postoperative patients. Neither primary endpoint for celecoxib was significantly different from placebo. Therefore this study cannot be used to support the claim that celecoxib is effective for acute pain in this model. Mean morphine consumption at 0-12 and 12-24 post surgery for celecoxib was numerically similar to placebo and thus celecoxib is not efficacious as a narcotic

sparing agent at early time points. **Nevertheless mean morphine and tramadol consumption at 24-36 hours was significantly less in the celecoxib group suggesting some efficacy in the "semi-acute" setting.** However, as noted by the sponsor, bolus injections of morphine were administered post-operatively while patients were asleep if the investigator judged that patient was in pain. This practice confounds the assessment of total opioid consumption in response to patient request for analgesia. The use of bolus doses in addition to PCA alone increases the "noise" in the system, since this practice varied from site to site. This adds further problems to the analysis of the results. Finally, small differences in narcotic consumption may have little clinical significance and the sponsor has not provided any evidence to support the clinical significance of these differences such as greater safety.

10. Trial 078

Multi-center double blind comparison of the analgesic effect of celecoxib 200 mg bid, diclofenac 75 mg SR bid, and placebo in patients with acute low back pain.

a. Objectives and rationale

The primary objective of this study was to evaluate the analgesic efficacy of celecoxib compared to placebo in the treatment of acute low back pain.

The secondary objectives of the study were to: 1) evaluate the analgesic efficacy of celecoxib compared to diclofenac, in the treatment of acute low back pain; 2) evaluate the analgesic efficacy of diclofenac compared to placebo in the treatment of acute low back pain; 3) compare placebo with celecoxib on the mobility of patients with acute low back pain using the Schober index; 4) compare placebo with celecoxib on the outcome of disability questionnaires performed at study days 1, 5, 10; 5) evaluate the safety of celecoxib compared to placebo and diclofenac in patients with acute low back pain.

b. Design

This was a multi-center double blind randomized active and placebo controlled parallel group comparison of the safety and analgesic effects of celecoxib 200 mg bid and diclofenac 75 mg SR bid compared to placebo orally administered to patients with acute low back pain. Patients with onset of back pain within 5 days and who met entry criteria were entered in to the study. They were followed for 10 days.

c.Protocol

1 Population and procedures

To qualify for the study the following criteria were used:
1. Been male or female, aged 18 to 65 years of age, inclusive.
2. For women of childbearing potential, confirmed use of adequate contraception, not been lactating, and had a negative pregnancy test (urine) at screening.
3. Presented with acute low back pain of either class 1a or 2a according to the Quebec Task Force Classification (Protocol).
4. Presented with an acute episode of moderate-severe (VAS >40 mm) low back pain.
5. Had the onset of the acute low back pain <5 days prior to inclusion in the trial and >6 weeks after the last episode.
6. A history of at least one reported episode of acute low back pain within the last 5 years.
7. Satisfactory health as determined by the Investigator on the basis of medical history and physical examination.
8. Provided written informed consent prior to undergoing any procedures in this study.

Candidates were not eligible for admission if they had any of the following:
1. Acute low back pain meeting any classification other than 1a or 2a on the Quebec Task Force Classification or neurologic in etiology.
2. A history of rheumatoid arthritis, ankylosing spondylitis, metastasis, Paget's disease, sciatica, psoriatic arthritis, fibromyalgia, or other diseases known to cause pain.
3. Moderate to severe scoliosis (> 40°).
4. Back pain due to major trauma (e.g. vertebral fracture or post-traumatic spondylolisthesis).
5. Back pain due to visceral disorder (e.g. dysmenorrhea or nephritic colitis).
6. Took a short-acting NSAID or an analgesic within the previous 8 hours, or a long-acting NSAID within the previous 48 hours of the screening visit for this study.
7. Unwilling to refrain from commencing concomitant physiotherapy including, but not limited to, transdermal electro neural stimulation (TENS), massage and spinal manipulation for the duration of the study period. Note: If the patient had had physiotherapy regularly for at least the last 4 weeks, prior to onset of latest acute low back pain episode, this therapy was permitted to continue this throughout the study.
8. A history of psychiatric disorder requiring treatment with anxiolytic and antidepressant medications.
9. A history of uncontrolled chronic disease that would, in the opinion of the Investigator, contraindicate study participation or confound interpretation of the results.
10. Any cognitive impairment that would, in the Investigator's opinion, preclude study participation or compliance with protocol-mandated procedures.
11. Active or suspected esophageal, gastric, pyloric channel, or duodenal ulceration or bleeding within 30 days prior to receiving the first dose of study medication.

12. Any known laboratory abnormality that would, in the opinion of the Investigator, contraindicate study participation, including aspartate transaminase (AST) or alanine transaminase (ALT) > 1.5, creatinine > 1.5, or urea > 1.5 times the upper limit of the reference range.
13. A history of known alcohol, analgesic, or narcotic abuse.
14. Known hypersensitivity to analgesics, NSAIDS, cyclooxygenase inhibitors, lactose, or sulfonamides.
15. Inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), a chronic or acute renal or hepatic disorder, a significant coagulation defect, or any condition that would, in the Investigator's opinion, preclude the use of an NSAID (e.g. congestive cardiac failure).
16. A history of asthma or bronchospasm.
17. A history of intolerance to diclofenac or paracetamol.
18. An active malignancy of any type, or a history of malignancy. (Patients with a history of basal cell carcinoma that was successfully treated were acceptable. Patients with a history of other malignancies, surgically removed with no evidence of recurrence for at least 5 years before enrollment in the study, were also acceptable.)
19. Received any investigational medication within 30 days prior to the first dose of study medication or was scheduled to receive an investigational drug other than celecoxib during the course of this study.
20. Were previously admitted to this study.

The study was double blind double dummy. The efficacy analyses were based on an ITT cohort.

2 Endpoints

The primary measures of efficacy were: 1) daily AUC for pain intensity; 2) maximum pain intensity; 3) minimum pain intensity; 4) time to reaching a pain free state; 5) variability in pain intensity; 6) assessment of trend in pain intensity.

The secondary measures of efficacy were: 1) global evaluation of study medication for pain; 2) time to first administration of rescue medication; 3) number of patients requiring rescue medication; 4) scores from the Schober index; 5) scores from the Roland Morris disability questionnaire.

3 Statistical considerations

AUC, pain intensity were analyzed by ANCOVA with treatment and center as factors and baseline pain as covariate. Global evaluation, Schober Index and Disability questionnaires were analyzed with a two way ANOVA. Number of patients who took rescue medication was analyzed by the CMH test. Log rank test was used to test for treatment differences.

A sample size of 50 patients in the placebo and 100 patients in each of the active treatment groups was chosen to detect a difference of .50 standard deviations with at least 80% power and an alpha level of .05 (two sided test).

d. Results

1 Patient disposition and comparability

Three hundred patients were enrolled and randomized to receive one of three treatments: 119 patients received celecoxib, 119 patients received diclofenac, and 62 received placebo. The treatment groups were comparable for age, race, gender, height and weight, blood pressure. Mean pulse showed a significant difference across treatment groups (p=.011).

The treatment groups were comparable for baseline pain intensity, although more patients in the placebo group reported severe pain (this was not significantly different however).

2 Efficacy endpoints outcomes

Analysis of primary measures of efficacy:

Mean daily AUC scores (categorical) for celecoxib were significantly different from placebo only on days 5 and 6. For diclofenac the differences were significant from days 2-10. Mean daily AUC scores (VAS) for celecoxib was significantly different from placebo on days 4,5,6. For diclofenac the differences were significant for days 2-10.

The mean daily maximum pain intensity scores (categorical) for celecoxib were significantly different from placebo on days 5,6,10. For diclofenac the differences were significant on days 3-10. The mean daily maximum pain intensity (VAS) for celecoxib was significantly different from placebo on days 3,4,5. For diclofenac the differences were significant on days 3-10.

The mean daily minimum pain intensity (categorical) scores for celecoxib were not different from placebo. For diclofenac the differences were significant on days 2-10. The mean daily minimum pain scores (VAS) for celecoxib were not different from placebo. For diclofenac the differences were significant on days 2-7,9,10.

The time to onset of a pain free state was no different between the celecoxib and placebo groups. However, for diclofenac the difference was significant.

Analysis of secondary measures of efficacy:

The mean patient global evaluation scores for celecoxib were significantly different from placebo on days 5 and 10 (p=.02 and .037 respectively). For diclofenac the differences were likewise significant (p=.002 and .001).

The time to first rescue medication showed no difference between groups. The number of patients requiring rescue medication showed no difference between groups.

There was no difference in the Schober Index between celecoxib and placebo, although the difference was significant for diclofenac (p=.015).

There was a significant difference between celecoxib and placebo for the mean scores of the Roland Morris Disability Questionnaire (p=.003 and .014). There was also a significant difference for diclofenac (p<.001 and p=.009).

e. Reviewer's comments

The primary measures of efficacy including the mean daily AUC and the mean maximum pain intensity scores were different from placebo only on isolated days starting at day 5. The other 2 primary measures of efficacy were not significantly different from placebo. Other measures suggest that celecoxib is more efficacious than placebo. Thus, this trial does not support the efficacy of celecoxib in the treatment of acute low back pain.

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## D. Efficacy conclusions

**Figure 79**: Summary of all studies in this sNDA along with the primary endpoints evaluated

| Primary Efficacy Variables | Post-Oral Surgery Pain, Postsurgical Pain, and Primary Dysmenorrhea Studies | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 025 | 027 | 070 | 005 | 139 | 085 | 086 | 082 | 028 | 080 | 083 | 029 | 129 | 130 |
| Median Time to Perceptible Pain Relief | √ | √ | √ | - | - | √ | √ | √ | - | √ | √ | - | - | - |
| Time-Specific PID (Categorical) | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | - | - |
| Time-Specific PR | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | - | - |
| Time Specific PRID | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | - | - |
| Median Time to Rescue Medication | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | - | - |
| SPID(8) (Categorical) | - | - | - | - | - | - | - | - | √ | - | - | √ | √ | √ |
| TOTPAR(8) | - | - | - | - | - | - | - | - | √ | - | - | √ | √ | √ |
| Median Time to Onset of Analgesia | - | - | - | - | √ | - | - | - | - | - | - | - | - | - |
| Median Time to Meaningful Pain Relief | - | - | - | - | - | - | - | - | √ | - | - | √ | - | - |
| SPID(8) (VAS) | - | - | - | - | - | - | - | - | √ | - | - | - | - | - |

Data derived from individual clinical study reports.

### A.Single dose assessment period studies

1. Post-dental surgery

Overall, on the basis of onset, magnitude, and duration of analgesia, single doses of celecoxib 200 mg and 400 mg exhibited consistent analgesic efficacy versus placebo in the post–oral surgery model and appeared superior to single doses of celecoxib 50 mg and 100 mg. Compared to lower doses, celecoxib 400 mg

provided onset and duration of analgesia to the highest percentage of patients, as well as the greatest magnitude of analgesia and confirmed celecoxib 400 mg as the maximally efficacious dose. Single doses of celecoxib 400 mg were comparable to naproxen sodium 550 mg in terms of time to onset, magnitude, and duration of analgesia, although the initial analgesic effect on the time-effect curves was less than the active comparator.

2. Dysmenorrhea

Results from the two primary dysmenorrhea studies demonstrate that single doses of celecoxib 400 mg are efficacious (based on onset, magnitude, and duration of analgesia) in the management of acute pain in this model. Also, the analgesic efficacy of celecoxib 400 mg was comparable to naproxen sodium 550 mg in terms of time to onset in both studies, and was generally comparable in magnitude and duration of analgesia in one of two studies.

In summary, in both the post-oral surgery and dysmenorrhea pain models the measures of analgesic action such as the time specific efficacy measures, duration of analgesia (as assessed by the time to rescue or remedication) and the time to onset of analgesia (using the stopwatch method), all appear to support the efficacy of celecoxib.

3. Post surgery pain studies

However, for a third pain model, post-surgical (orthopedic/general) pain (studies 082,083,085,086,028), studies do not support the efficacy of single doses of celecoxib (200 mg) for acute pain (celecoxib 400 mg was not used as the initial dose in any of these studies). For example, the time specific efficacy measures do not consistently separate from placebo especially at the earlier time points. In study 082 mean PID scores for celecoxib were significantly different from placebo only at the 3-5 hour assessment. In study 085 differences occurred at the 2-8 hour assessment. The difference in time to rescue medication between celecoxib and placebo was significant in 2 studies but not in the other 2. The time to onset of perceptible pain relief was not significantly different in any study.

As part of the analysis of studies 085 and 086 the sponsor performed a post hoc analysis on the pooled populations. This was based on the fact that both protocols were identical and that pooling of patients would provide the study with a greater power to detect differences between placebo and treatment. While it is true that pooling studies may lead to a greater power to detect statistical differences, these differences may no longer be clinically meaningful especially as it relates to pain management.

Baseline demographic data for the pooled populations demonstrated no significant differences between the groups. For the pooled studies, the following were significantly different comparing

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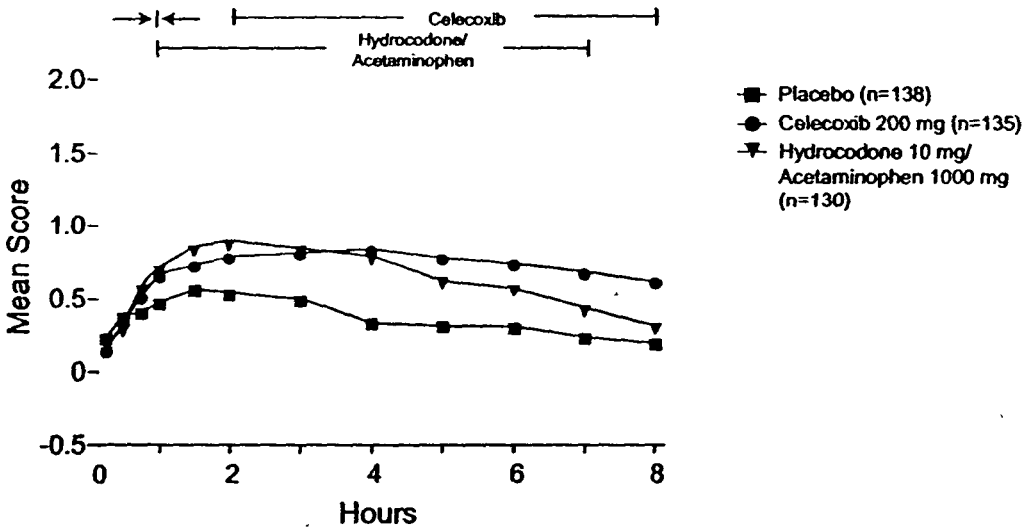
**Figure 80: Mean PID for pooled studies**




celecoxib and placebo: median time to onset of analgesia (previously defined as a secondary endpoint); SPID (8) and TOTPAR (8) (secondary endpoints); median time to rescue medication. In addition, time specific efficacy measures PID and PRID were now significant at the 1 and 2-8 hour assessments while PR was significant at the 3-8 hour assessments. Examples of results for pooled studies for PID and PRID are shown (see Figures 80 and 81).

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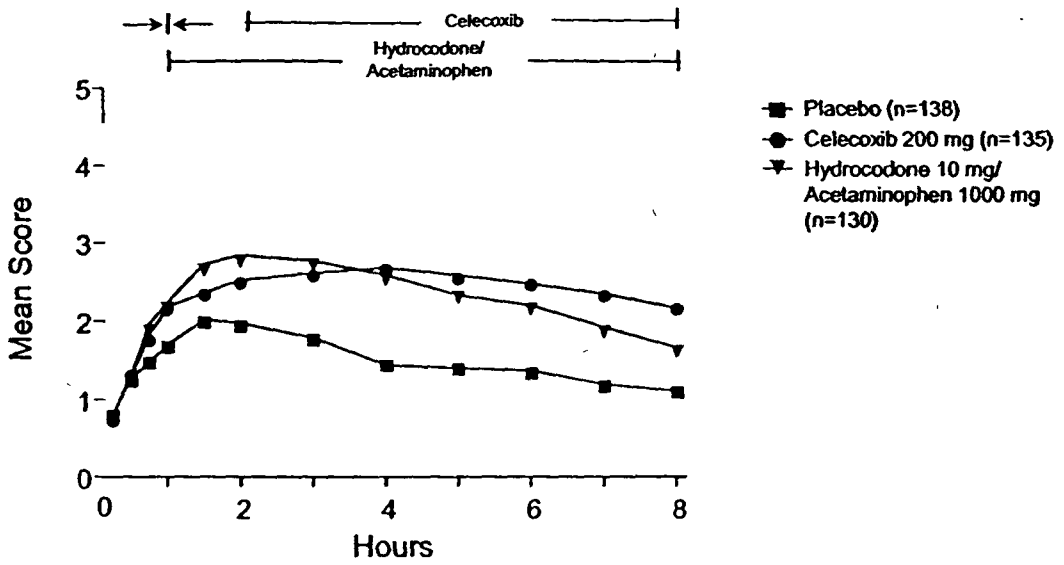
**Figure 81**: Mean PRID for pooled studies




In summary, the data do not support the efficacy of single doses of celecoxib in the treatment of acute pain in this model and pooling of data while providing improved power may lead to conclusions that are no longer clinically meaningful.

B Multiple Dose Assessment Period studies

While celecoxib appears efficacious as a single dose, there is some concern regarding the use of celecoxib for acute pain because of the limited efficacy data supporting the short term use of the drug.

Study 028 previously reviewed, did not present any consistent evidence of superior efficacy of celecoxib over placebo in the multiple dose period. Studies 029 and 080 were not reviewed for reasons presented in the original NDA submission. Studies 074 and 075 were not considered pivotal studies but are reviewed. However, confidence in the results of these two studies is limited because of problems with the study design as described above.

However, study 074, a non-pivotal study in post-surgical pain, was suggestive of efficacy in the multiple dose period. The mean scores of pain intensity assessments on days 2-4 were significantly different favoring celecoxib over placebo. The mean maximum pain intensity scores for celecoxib were significantly different from placebo on days 2-4 (but not day 1). The mean patient Global Evaluation scores for the celecoxib 200 mg BID treatment group were numerically higher than the placebo treatment group on all four study days. For the pairwise comparisons, these differences were statistically significant on study

days 2 (p=0.003), 3 (p=0.005), and 4 (p=0.009). For study 075, the mean morphine consumption from 24-36 hours post-surgery for the celecoxib 200 mg BID treatment group (6.0 mg) was lower than the placebo treatment group (9.0 mg); this was a statistically significant difference (p=0.027).

The results of studies 129 and 130 for dysmenorrhea for the multiple dose period were inconclusive due to high patient dropout after the single dose period. Some trends suggesting efficacy in the multiple dose period include a numerically superior patient global assessment for celecoxib over placebo as well as a slightly lower pain intensity score before each dose in study 129. In study 130 patient global evaluation was numerically greater for celecoxib over placebo.

Studies 085 and 086 both had multiple dose assessment periods. In both studies a placebo group was not continued through the multiple dose period. In study 086 the positive comparator did not separate from placebo even in the single dose period and therefore a comparison of celecoxib to the positive comparator in the multiple dose period is problematic. It might have been possible to draw conclusions from this MDAP if celecoxib had been clearly significantly superior to hydrocodone for the MDAP, but this was not the case. Celecoxib was superior to hydrocodone for days 2-5 for: number of doses of study medication taken, mean maximum pain intensity scores, and predose pain intensity for days 3 and 4 only. For other measures there was no difference between celecoxib and hydrocodone.

This leaves only study 085 with a multiple dose study period that can be further evaluated. The outcomes of the following endpoints described in the protocol were significantly different favoring celecoxib over the positive comparator: the number of patients who dropped out due to treatment failure/rescue medication, the mean maximum pain intensity scores, the response to the APS questions, and the mean patient global evaluation (see Figures 82 and 83).

The mean Pain Intensity scores for the celecoxib treatment group before doses 1, 2, or 3, on Day 2 were lower than those for the hydrocodone treatment group. These differences were statistically significant for the first and second doses of study medication. For Day 3 the mean Pain Intensity scores for the treatment group before doses 1, 2, and 3, were lower than those for the hydrocodone treatment group. These differences were statistically significant for all three doses of study medication. For Days 4 and 5 the mean Pain Intensity scores for the celecoxib treatment group before doses 1, 2, and 3, were numerically less than those for the hydrocodone treatment group. None of these differences were statistically significant.

The following were not different between the 2 treatment groups: time between two consecutive doses on day 2 through day 5; number of doses of study medication taken on day 2 through day 5; mean maximum pain relief scores.

Figure 82: Mean maximum pain intensity for pooled studies

| Study Treatment | Maximum Pain Intensity | | | |
|---|---|---|---|---|
| | Day 2 | Day 3 | Day 4 | Day 5 |
| **Study 085** | | | | |
| Celecoxib | 1.70 | 1.30 | 1.14 | 0.97 |
| Hydrocodone/ Acetaminophen | 2.17 | 1.90 | 1.69 | 1.62 |
| p-value | <0.001 | <0.001 | <0.001 | <0.001 |
| **Study 086** | | | | |
| Celecoxib | 1.72 | 1.40 | 1.35 | 1.18 |
| Hydrocodone/ Acetaminophen | 1.99 | 1.82 | 1.69 | 1.56 |
| p-value | 0.032 | 0.002 | 0.016 | 0.009 |
| **Studies 085/086** | | | | |
| Celecoxib | 1 71 | 1.35 | 1.25 | 1.08 |
| Hydrocodone/ Acetaminophen | 2.07 | 1.86 | 1.69 | 1.59 |
| p-value | <0.001 | <0 001 | <0 001 | <0.001 |

Source: Appendix 6.1.2.

Figure 83 shows the Response to APS questions for studies 085,086 and pooled studies

| Study Treatment | Pain Now | Worst Pain in Past 4 Days | Average Pain in Past 4 Days | Composite Pain Interference |
|---|---|---|---|---|
| **Study 085** | | | | |
| Celecoxib | 2.0 | 5.5 | 3.3 | 18.4 |
| Hydrocodone/ Acetaminophen | 3.5 | 6.8 | 4.2 | 26.6 |
| p-value | <0.001* | 0.007* | 0.010* | 0.001* |
| **Study 086** | | | | |
| Celecoxib | 2.2 | 5.4 | 3.0 | 17.2 |
| Hydrocodone/ Acetaminophen | 2.9 | 6.3 | 3.9 | 23.1 |
| p-value | 0.063 | 0.027* | 0.007* | 0.015* |
| **Studies 085/086** | | | | |
| Celecoxib | 2.1 | 5.5 | 3.2 | 17.8 |
| Hydrocodone/ Acetaminophen | 3.2 | 6.6 | 4.1 | 24.8 |
| p-value | <0.001* | <0.001* | <0.001* | <0.001* |

* Statistically significant at the 0.05 level.
Source: Appendix 6.1.3.

As previously discussed, as part of the analysis of studies 085 and 086 the sponsor

performed a post hoc analysis on the pooled populations, and while it is true that pooling studies may lead to a greater power to detect statistical differences, these differences may no longer be clinically meaningful. Furthermore, the positive comparator failed (did not differ from placebo) in study 086. Because of the above, studies 085 and 086 should not be combined for the multiple dose assessment period as the sponsor has attempted.

Therefore, the efficacy of celecoxib for the multiple dose period may be supported by the results of some of the studies described. **Nevertheless, there are difficulties in evaluating the multiple dose assessment period in each study. It appears that the most significant problem is related to the high drop-out rate in these models due to a rapidly decreasing pain intensity, rather than to lack of efficacy. Presumably any analgesic that is effective for acute pain as a single dose will also be effective when taken as multiple doses over short time periods for acute pain that is resolving (such as occurs in the models studied). However, determining the dosing interval without multiple dose periods may be problematic (see discussion of dosing interval). Nevertheless, specifically for celecoxib there is already a considerable amount of data supporting chronic use and appropriate dosing intervals, albeit for different models of pain (rheumatoid arthritis and osteoarthritis).**



## VII. Integrated Review of Safety

### A. Conclusions

Celecoxib has previously been approved for chronic use for the signs and symptoms of OA and RA. The prescribing information details contraindications, warnings, precautions, adverse reactions and over doses. There are no new significant concerns raised by the present submission. The only new adverse reaction not previously associated with the use of celecoxib is termed alveolar osteitis ("dry socket") occurring in the post-dental pain models. This is likely not related to the drug per se but secondary to the dental surgery.

### B. Patient exposure by dose

**Figure 84:Summary of unique patients in celecoxib pain studies**

| Placebo | Celecoxib | | | | | | | Active Control‡ |
|---|---|---|---|---|---|---|---|---|
| | Single Dose | | | | | | Multiple Dose | |
| | 25 mg | 50 mg | 100 mg | 200 mg | 200 mg† | 400 mg | | |
| 816 | 50 | 85 | 155 | 203 | 53 | 85 | 1088 | 965 |

Derived from Table T2.6.
†Suspension formulation; all other celecoxib doses are capsule formulations.
‡Includes celecoxib 200 mg per day, 2 doses (100 mg or 200 mg) per day PRN, and 200 mg BID or TID PRN treatment groups.

Only about 13% of patients received the highest dose of 400mg.

**Figure 85: Patient exposure by dose and duration**

| | | Celecoxib | | | | | |
|---|---|---|---|---|---|---|---|
| Studies | placebo | 25mg | 50mg | 100-200mg | 200mg suspension | 400mg | Active control |
| dental | | | | | | | |
| 1 day | 256 | 50 | 85 | 360 | 53 | 85 | 241 |
| 2-7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Post-surg | | | | | | | |
| 1 day | 313 | | | 274 | | | 206 |
| 2-5 | 54 | | | 224 | | | 198 |
| >5 | 8 | | | 42 | | | 27 |
| Dysmen. | | | | | | (400/200 mg) | |
| 1 day | 233 | | | | | 200 | 200 |
| 2-7 | 23 | | | | | 53 | 51 |
| Europe. surgical | | | | | | | |
| 1 day | 3 | | | 9 | | | 8 |
| 2-5 | 88 | | | 167 | | | 176 |
| >5 | 84 | | | 166 | | | 165 |

*The majority of patients took celecoxib for only one day. Relatively few patients are treated for more than 5 days.*

**C. Methods and specific findings of safety review**

There were no studies designed to specifically address safety issues in this submission. The CLASS trial (not a part of this sNDA) studied GI safety using 2-4x dose of celecoxib. The primary endpoints for GI safety comparing celecoxib to 2 NSAID comparators (diclofenac and ibuprofen) were not met in this trial.

**D. Adequacy of safety testing**

For the indications proposed in this submission, the safety testing appears to be adequate. However, most individuals in the dysmenorrhea and oral surgery studies are young and in relatively good health. It is not anticipated that patients with acute pain or dysmenorrhea will take celecoxib for prolonged periods of time (in excess of 5 days). In the studies performed, symptoms of acute pain and dysmenorrhea resolved over a relatively short period of time, usually no longer

than 5 days. Longer term studies at 100-200 mg bid have already been performed and reviewed. Finally, the CLASS trial examined doses at 2-4x the recommended dose for up to one year. Therefore, it does not appear that additional studies are needed to resolve most concerns. One area of future investigation relates to the risk of thromboembolic problems with the use of Cox-2 inhibitors.

**E. Significant/potentially significant events**

1. deaths

A single death occurred during these clinical trials. In study 082 a 64 year old male expired 11 days after surgery. An autopsy demonstrated coronary atherosclerosis. The patient was randomized to receive hydrocodone.

2. other significant events

Serious adverse events occurred in about 1-2% of patients.



**Figure 86: Serious Adverse Events occurring in at least 2 patients in all surgical studies combined**

| Event | Placebo* | Celecoxib | Opioids/NSAID's |
|---|---|---|---|
| Number treated | 488 | 716 | 605 |
| Any event | 12/13 | 9/12 | 14/20 |
| Cellulitis | 0/0 | 0/0 | 2/2 |
| CAD | 0/0 | 0/0 | 2/2 |
| Infection | 1/1 | 2/2 | 2/2 |
| Fever | 2/2 | 0/0 | 0/0 |
| Urinary retention | 0/0 | 1/1 | 1/1 |
| Hematoma | 1/1 | 0/0 | 1/1 |
| Thrombophlebitis | 0/0 | 1/1 | 1/1 |

*Data represents number of patients/number of episodes

In the oral surgery studies a single patient who received a single dose of celecoxib withdrew from the study after he was diagnosed with rectal carcinoma.

No serious adverse events were reported in the musculoskeletal study.
A total of 2 patients experienced 2 adverse events in the dysmenorrhea studies, one in the placebo group and the other in the opioid group. Both were unintended pregnancies.

3. drop outs

**Figure 87:Adverse Events causing withdrawal with incidence >1% in postsurgical and musculoskeletal studies combined (numbers of patients with each adverse event)**

| Adverse Event | Placebo | Celecoxib | Opioid | NSAID |
|---|---|---|---|---|
| Number treated | 1081 | 1473 | 809 | 590 |
| Any Event | 21 | 40 | 18 | 20 |
| Headache | 3 | 6 | 2 | |
| Nausea | | 5 | 6 | 5 |
| Vomiting | 4 | 2 | 6 | |
| Infection | 1 | | | |
| Sweating increased | 1 | | | |
| Fever | 2 | | | 1 |
| Dizziness | 1 | 1 | | |
| Abdominal pain | | 2 | | 6 |
| CVA | 1 | | | |
| Neuralgia | 1 | | | |
| Arthrosis | 1 | | | |
| Rash | 1 | | | |

*GI and CNS events are the most common adverse events causing dropout and are already recognized as problems with celecoxib (see also below).*



**Figure 88**: Adverse events causing withdrawal in dental surgery (incidence >1%)

| Adverse Event | Placebo | Celecoxib | | | | | | NSAIDs[‡] |
|---|---|---|---|---|---|---|---|---|
| | | 25 mg | 50 mg | 100 mg | 200 mg | 200 mg[†] | 400 mg | |
| No. Treated | 256 | 50 | 85 | 155 | 205 | 53 | 85 | 241 |
| Any Event | 0.0 | 0.0 | 1.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| [redacted] | | | | | | | | |
| Oral hemorrhage | 0.0 | 0.0 | 1.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |

Derived from Table T5.4. Data represent % patients unless otherwise indicated.
[†] Suspension formulation; all other celecoxib doses are capsule formulations.
[‡] Include aspirin 650 mg, ibuprofen 400 mg, and naproxen sodium 550 mg treatment groups.

In the dental surgery group only oral hemorrhage caused dropout.
In the dysmenorrhea studies, the only adverse event causing withdrawal occurred during naproxen sodium treatment, in which one (0.4%) patient reported an unintended pregnancy.

4. overdose exposure

There were no reports of celecoxib overdose in these pain studies. In arthritis studies one patient was identified who inadvertently took significantly elevated doses of study drug. There were no signs or symptoms suggestive of drug overdose and no medical management was needed.

5. other safety findings

a. ADR incidence tables-most common adverse events

*In general, GI and CNS appear to be the most common adverse events reported, and these are well recognized from previous trials.*

Figure 89: Adverse events in European post-hip replacement studies

**Table 19.o. Adverse Events with Incidence ≥3% in Any Treatment Group: European Post-Hip Replacement Pain Study**

| Adverse Event | Placebo | Celecoxib 200 mg BID | Diclofenac SR 75 mg BID |
|---|---|---|---|
| No. Treated | 56 | 111 | 116 |
| Any Event | 87.5 | 78.4 | 74.1 |
| Hypertension | 7.1 | 7.2 | 6.9 |
| Hypotension | 1.8 | 3.6 | 0.9 |
| Back pain | 3.6 | 2.7 | 0.9 |
| Chest pain | 3.6 | 1.8 | 0.9 |
| Fever | 28.6 | 12.6 | 11.2 |
| Dizziness | 3.6 | 5.4 | 2.6 |
| Headache | 7.1 | 6.3 | 1.7 |
| Abdominal pain | 5.4 | 5.4 | 8.6 |
| Constipation | 18.1 | 14.4 | 6.9 |
| Diarrhea | 0.0 | 0.9 | 7.8 |
| Nausea | 30.4 | 36.0 | 37.1 |
| Vomiting | 26.8 | 21.6 | 20.7 |
| Tachycardia | 5.4 | 0.9 | 1.7 |
| Hepatic function abnormal | 1.8 | 3.6 | 6.0 |
| SGOT increased | 5.4 | 0.0 | 5.2 |
| SGPT increased | 5.4 | 0.9 | 5.2 |
| Hypokalemia | 0.0 | 3.6 | 2.6 |
| Phosphatase alkaline increased | 5.4 | 0.9 | 2.6 |
| Bleed, incisional | 1.8 | 0.0 | 4.3 |
| Anorexia | 3.6 | 1.8 | 0.9 |
| Insomnia | 3.6 | 3.6 | 6.9 |
| Anemia | 10.7 | 6.3 | 12.1 |
| Dyspnea | 7.1 | 0.9 | 0.9 |
| Rash | 3.6 | 0.9 | 0.0 |
| Sweating increased | 1.8 | 3.6 | 0.0 |
| Oliguria | 3.6 | 4.5 | 6.0 |
| Urinary retention | 1.8 | 6.3 | 7.8 |

Derived from Table T8.2. Data represent % patients unless otherwise indicated.

*There was more nausea in the celecoxib group but more vomiting in the placebo group.*

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**Figure 90: Adverse events in post-oral surgery studies**

**Table 10.a. Adverse Events with Incidence ≥3% in Any Treatment Group: Post-Oral Surgery Pain Studies**

| Adverse Event | Placebo | Celecoxib | | | | | | NSAIDs[2] |
|---|---|---|---|---|---|---|---|---|
| | | 25 mg | 50 mg | 100 mg | 200 mg | 200 mg[1] | 400 mg | |
| No. Treated | 256 | 50 | 85 | 155 | 205 | 53 | 85 | 241 |
| Any Event | 46.9 | 46.0 | 47.1 | 31.6 | 53.7 | 58.5 | 35.5 | 44.4 |
| Asthenia | 0.8 | 4.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Fever | 0.4 | 2.0 | 0.0 | 0.0 | 2.0 | 3.8 | 0.0 | 1.2 |
| Influenza-like symptoms | 0.0 | 0.0 | 0.0 | 0.6 | 1.5 | 3.8 | 0.0 | 0.0 |
| Dizziness | 7.0 | 4.0 | 7.1 | 5.2 | 5.4 | 1.9 | 0.0 | 5.0 |
| Headache | 16.8 | 12.0 | 8.2 | 8.4 | 15.6 | 24.5 | 7.1 | 16.2 |
| Paresthesia | 1.6 | 0.0 | 0.0 | 0.6 | 2.4 | 11.3 | 1.2 | 2.9 |
| Intermenstrual bleeding | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 6.5 | 0.0 | 0.0 |
| Alveolar osteitis | 9.8 | 18.0 | 17.6 | 8.5 | 12.7 | 7.5 | 9.4 | 9.1 |
| Nausea | 11.7 | 12.0 | 14.1 | 8.4 | 14.6 | 13.2 | 8.2 | 14.1 |
| Vomiting | 6.6 | 6.0 | 3.5 | 3.9 | 3.9 | 3.8 | 2.4 | 5.8 |
| Earache | 3.5 | 0.0 | 0.0 | 0.6 | 2.4 | 5.7 | 1.2 | 0.8 |
| Oral hemorrhage | 0.0 | 0.0 | 3.5 | 0.6 | 0.5 | 0.0 | 1.2 | 0.4 |
| Somnolence | 1.2 | 2.0 | 2.4 | 3.9 | 2.9 | 0.0 | 4.7 | 1.7 |
| Rhinitis | 1.6 | 0.0 | 0.0 | 0.6 | 1.0 | 3.8 | 0.0 | 0.8 |
| Skin discoloration | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 3.8 | 0.0 | 0.4 |

Derived from Table T5.2. Data represent % patients unless otherwise indicated.
[1] Suspension formulation; all other celecoxib doses are capsule formulations.
[2] Include aspirin 650 mg, ibuprofen 400 mg, and naproxen sodium 550 mg treatment groups.

There was an increasing incidence of headaches as the dose of celecoxib was increased except at the highest dose (at 400 mg only 7.1% headaches). Other adverse events did not show any dose response.

**Figure 91: Adverse events in primary dysmenorrhea studies**

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**Table 10.t. Adverse Events with Incidence ≥3% following Treatment: Primary Dysmenorrhea Studies**

| Adverse Event | Placebo | Celecoxib[1] | Naproxen Sodium[2] |
|---|---|---|---|
| No. Treated | 256 | 253 | 251 |
| Any Event | 30.5 | 31.2 | 36.3 |
| [redacted] | | | |
| Dizziness | 1.6 | 1.8 | 3.6 |
| Headache | 3.9 | 3.6 | 5.2 |
| [redacted] | | | |
| Nausea | 2.7 | 4.3 | 4.0 |

Derived from Table T10.2. Data represent % patients unless otherwise indicated.
[1] Patients received an initial dose of celecoxib 400 mg, a second dose of celecoxib 200 mg, and subsequent doses of celecoxib 200 mg every 12 hours PRN thereafter.
[2] Patients received an initial dose of naproxen sodium 550 mg, followed by naproxen sodium 550 mg every 12 hours PRN thereafter.

*CNS and GI are the most frequent cause of adverse events.*

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**Figure 92**: Adverse events in post-surgical studies (single and multiple dose)

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**Table 10.c. Adverse Events with Incidence ≥3% in Any Treatment Group: North American/New Zealand Postsurgical Pain Single-Dose and Multiple-Dose Study Periods**

| Adverse Event | Placebo | Celecoxib[1] | Opioids[2] |
|---|---|---|---|
| No. Treated | 375 | 493 | 375 |
| Any Event | 38.7 | 40.4 | 53.9 |
| Fever | 5.9 | 2.4 | 2.9 |
| Dizziness | 3.7 | 3.4 | 9.1 |
| Headache | 5.9 | 6.5 | 7.7 |
| Dyspepsia | 0.8 | 3.2 | 1.9 |
| Nausea | 9.9 | 10.8 | 15.7 |
| Vomiting | 4.8 | 5.9 | 8.0 |
| Somnolence | 3.7 | 4.5 | 12.0 |

Derived from Tables T6.2. Table includes events in Studies 028, 029, 080, 082, 083, 085, and 086. Data represent % patients unless otherwise indicated.
[1] Includes celecoxib 200 mg per day, 2 doses (100 mg or 200 mg) per day PRN, and 200 mg BID or TID PRN treatment groups.
[2] Include propoxyphene napsylate 100 mg/acetaminophen 650 mg and hydrocodone 10 mg/acetaminophen 1000 mg treatment groups, a single patient in Study 080 who received naproxen 500 mg, but who did not have any adverse event, is included in this category

*CNS and GI are again the most frequent cause of adverse events.*

b. Adverse events summarized by study:

Study 139:
Adverse events were reported for 37/51 (72.5%) of patients in the placebo group, for 31/53 (58.3%) of patients in the celecoxib suspension group, for 39/49 (79.6%) of patients in the celecoxib capsule group, and for 39/49 (79.6%) of patients in the ibuprofen group. **An adverse event not previously reported with celecoxib was alveolar osteitis. However the incidence of this was no different than placebo and was likely related to the surgical procedure and not a consequence of the drug.** There were no serious adverse events, deaths, or adverse events causing withdrawal from the study. There were no changes in laboratory values, physical examination, or vital signs that appear to be systematically related to the study medication. **One patient had an elevated CPK (690 U/L at 24 hours), but no further information is provided.**

Study 129:
Adverse events were reported for 38 of 127 (29.9%) patients in the placebo group, 39 of 129 (30.2%) in the celecoxib group, and 46 of 126 (36.5%) in the naproxen group. Gastrointestinal disorders did not show a significantly higher incidence in the active versus placebo treated groups, although there was a slightly higher

incidence of constipation and nausea. There was no dyspepsia reported. No adverse events were indicative of hepatic, renal, or platelet dysfunction. No reports of thrombotic events were noted. There was a pregnancy during the study which led to withdrawal from the study. One patient during the final placebo treatment period had an incident of extreme urine RBC value.

Study 130:
There were no adverse events causing withdrawal. There were three pregnancies reported as serious adverse events. The most common adverse events were headache, nausea, and increased sweating. Diarrhea and nausea were the only GI events noted. Extreme laboratory values were reported for urine protein, RBC, and WBC.

Study 082:
Adverse events were reported by 18 (27%) of patients receiving placebo, 17 (24%) of patients receiving celecoxib, and 28 (42%) of patients receiving hydrocodone. GI and CNS/psychiatric disorders were the most commonly reported with no differences between the groups except for an increase of CNS disorders especially somnolence in the hydrocodone group. Five patients withdrew from the study due to adverse events and only one was in the celecoxib group (leg cramps). There were 5 SAE's including one death all of whom received hydrocodone.

Study 083:
Adverse events were reported by 34 (51%) of patients in the placebo group, 28 (42%) of patients in the celecoxib treated group, and 37 (56%) of patients in the hydrocodone group. The most common adverse events by system include GI and CNS/psychiatric. The most common GI adverse events reported were nausea and vomiting. Somnolence was reported by 11 (17%) of patients on hydrocodone, 2 (3%) of patients on celecoxib, and 7 (10%) of patients on placebo. No patient in the celecoxib treatment group withdrew due to an adverse event.

Three patients developed a serious adverse event. No SAE was reported in the celecoxib treatment group.

Study 085:
Adverse events in the SDAP were reported by 16 (23%) of the patients receiving placebo, 13 (19%) of patients receiving celecoxib and 19 (31%) of the patients receiving hydrocodone. The most frequent adverse events were nausea, somnolence, vomiting, dizziness, headaches, dry mouth and pruritus. Two patients in the celecoxib treated group reported severe nausea or nausea and vomiting. However, no patient withdrew from the SDAP as a result of a adverse event. Three patients reported severe CNS events including headache in one placebo and one celecoxib treated individual, and paresthesias in one hydrocodone treated patient.

In the MDAP adverse events were reported by 38 (43%) of patients receiving celecoxib, and 55 (68%) of patients receiving hydrocodone. The most common adverse events were headache, nausea, somnolence, dizziness, dry mouth, nervousness, increased sweating, and vomiting.

A total of 6 patients withdrew from the study due to adverse events, three in the celecoxib treated group and 3 in the hydrocodone treated group. There were no serious adverse events reported.

The only clinically relevant laboratory result reported by 5% or more of patients was reduced hematocrit ( 8 (12%) placebo, 8(12%) celecoxib and 3(5%) hydrocodone and hemoglobin ( 3 (5%) placebo, 2 (3%) celecoxib, and 2 (3%) hydrocodone). There were additional laboratory changes of statistical significance but of unlikely clinical significance.

Study 086:
For the SDAP adverse events were reported by 14 (19%) of patients in the placebo group, 13 (18%) of patients in the celecoxib group, and 15 (20%) of patients in the hydrocodone group. The most frequent adverse events were nausea and dizziness. For the MDAP adverse events were reported by 34 (39%) of patients in the celecoxib group and 51(53%) of patients in the hydrocodone group. The most frequent adverse events were nausea, dyspepsia, headache, somnolence, vomiting, dizziness and constipation. The overall difference in adverse events between celecoxib and hydrocodone was significant (p=.027).

For the SDAP only one patient in the hydrocodone group withdrew because of an adverse event (dizziness). For the MDAP only one patient withdrew due to an accidental injury following a fall; 5 patients in the hydrocodone group withdrew due to dermatitis, rash, and 3 for nausea.

A total of two patients (one in each group celecoxib and hydrocodone) reported a total of 5 serious adverse events. These included gangrene and osteomyelitis for the celecoxib group and nausea and vomiting and serous wound drainage in the hydrocodone group. There were no deaths during the study.

The only clinically relevant laboratory changes were reduced hematocrit (10 (16%) placebo, 13 (18%) celecoxib, and 19 (25%) hydrocodone group) and hemoglobin. A number of additional laboratory changes occurred but were likely not of clinical significance.

There were no significant differences between groups in any of the vital signs measured.

Study 074:
Adverse events were reported by 29 (51%) of patients receiving placebo, 32 (29%) of patients receiving celecoxib, and 36 (32%) of the patients receiving

diclofenac. The most common events included nausea, constipation, dizziness, vomiting, diarrhea, fever, hypotension, urinary retension, headache, dyspepsia, hematoma, hepatic function abnormal, rash, and abdominal pain.

A total of 7 patients withdrew due to 11 adverse events: 3 (5%) patients in the placebo group (nausea, infection, sweating increased, vomiting), 1 (<1%) patient in the celecoxib group (dyspnea and hypotension), and 3 (#%) patients in the diclofenac group (abdominal pain, diarrhea, dizziness, urinary retention).

Serious adverse events were reported by 6 (11%) of patients receiving placebo, 2 (2%) of patients receiving celecoxib and 2 (2%) of patients receiving diclofenac. There were no deaths during the study.

Study 075:
Adverse events were reported by 49 (88%) of patients receiving placebo, 87 (78%) of patients receiving celecoxib and 86 (74%) of patients receiving diclofenac. The most common adverse events were nausea, vomiting, constipation, fever, hypotension, anemia, urinary retention, headache, abdominal pain, dizziness, oliguria, abnormal hepatic function . **Adverse events related to angina and myocardial ischemia were see in 3 patients all of whom received celecoxib.**

A total of 21 patients withdrew form the study due to one or more adverse events: 4 (7%) in the placebo group, 6 (5%) in the celecoxib group, and 11 (9%) in the diclofenac group. Serious adverse events were reported by 1 (2%) of patients in the placebo group, 3 (3%) of patients receiving celecoxib, and 2 (2%) of patients receiving diclofenac. There was one death in the study in the placebo group following a stroke and sepsis.

Study 078:
A total of 300 patients were randomized into the study with all receiving at least one dose of study medication as follows: 62 receiving placebo, 119 receiving celecoxib and 119 receiving diclofenac.

Adverse events were reported by 9 (15%) of patients receiving placebo, 20 (17%) of patients receiving celecoxib and 9 (15%) of patients receiving diclofenac. The most common adverse events were abdominal pain, diarrhea, nausea, headache, paresthesias, gastritis, dizziness, flatulence, leukocytosis, and increased sweating.

A total of 11 patients withdrew from the study due to 14 adverse events: 2 (3%) in the placebo groups, 3 (3%) in the celecoxib groups, and 6 (5%) in the diclofenac group.

No serious adverse events or deaths were reported during this study.

c. laboratory findings, vital signs

Pulse rate and BP changes are statistically different comparing celecoxib to placebo. These differences are probably of little clinical significance.

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**Figure 93: Incidence of Extreme Lab Values and Vital Signs>1% in any Treatment Group**

| Lab test | placebo | celecoxib | NSAID | Opioid | p-Value | | |
|---|---|---|---|---|---|---|---|
| | | | | | Celecoxib versus placebo | Celecoxib versus NSAID | Celecoxib versus Opioid |
| Total bili above 35umol/L | 2/253 | 9/287 | 2/232 | | .068 | .122 | |
| Lymphocyte count $<10^9$/L | 4/243 | 2/428 | 1/336 | | .197 | | |
| PTT above 59 seconds | 0/45 | 3/83 | 0/92 | | | .105 | |

| Vital signs | | | | | | |
|---|---|---|---|---|---|---|
| Diastolic BP, 15% decrease from baseline | 27/248 | 30/280 | 13/232 | | .039 | |
| Pulse rate, 15% increase from baseline | 66/248 | 59/280 | 55/232 | .151 | | |
| Diastolic BP 15% increase from baseline | 2/56 | 17/112 | 19/114 | .036 | | |
| Pulse rate,15% decrease from baseline | 22/347 | 50/484 | 33/369 | .046 | | |
| Pulse rate 15% increase from baseline | 55/347 | 56/484 | 59/369 | .079 | | .069 |
| Male weight 5% decrease from baseline | 0/8 | 2/20 | 0/27 | | .176 | |

Comparing celecoxib to placebo, elevated total bilirubin and pulse rate increase approach statistical significance, and diastolic BP increase is less than .05 (Figure 93). The change of pulse rate is not consistent.

**Figure 94: Summary table**

**Table 13.c. Summary of Hematologic, Hepatobiliary, and Renal Contingency Laboratory Tables: North American/New Zealand Postsurgical Pain Studies**

| Combination | Placebo | Celecoxib[1] | Opioids[2] |
|---|---|---|---|
| Hemoglobin decrease ≥2 and Hematocrit >10% | 3/225 | 2/400 | 0/325 |
| SGOT ≥3xULN and SGPT ≥3xULN | 2/246 | 2/443 | 3/348 |
| Creatinine ≥159 µmol/L and BUN 14.3 ≥µmol/L | 0/257 | 0/451 | 0/352 |
| Alkaline phosphatase ≥3xULN and Bilirubin ≥1 8xULN | 0/245 | 0/438 | 0/344 |
| SGPT ≥3xULN and Alkaline phosphatase ≥3xULN | 1/245 | 0/439 | 0/344 |
| SGPT ≥3xULN and Bilirubin ≥1 8xULN | 0/248 | 1/443 | 0/346 |

Derived from Tables T16.4.1 through T16.4.6. Data represent number of patients with values/number of patients tested.
[1] Includes celecoxib 200 mg per day, 2 doses (100 mg or 200 mg) per day PRN, and 200 mg BID or TID PRN treatment groups.
[2] Include propoxyphene napsylate 100 mg/acetaminophen 650 mg and hydrocodone 10 mg/ acetaminophen 1000 mg treatment groups, a single patient in Study 080 who received naproxen sodium 500 mg, but who did not have any adverse event, is counted in this category.

One individual developed an elevated SGPT and bilirubin (was a 38-year-old female (Patient No. 0332) who was enrolled in Study 029 and received celecoxib 200 mg for one day; the patient was noted to have elevation of liver enzymes prior to study medication and was discontinued from the study); 2 additional patients developed an elevated SGOT and SGPT >3x normal. There were no serious adverse hepatobiliary or renal events reported (Figure 94).

4. Review of systems and special studies

a. Vascular

There has been some concern expressed about the relationship of Cox-2 inhibitors and cardiovascular disease. There were no vascular or vaso-occlusive adverse events in the post-oral surgery studies. There were no vascular events in the dysmenorrhea studies that occurred with an incidence of >.5%, and there were no events reported in the celecoxib group. However, these groups are likely to contain individuals at low risk for these complications.

The incidence of vascular events in the postsurgical studies is provided below in Figures 95 and 96. There were no MI's reported in patients on celecoxib. *Overall, the incidence of cardiovascular adverse events appears to be low and no different from the incidence in other treatment groups, although there were no cardiac events in the placebo group.* In the recent CLASS safety trial powered to look at GI safety (not powered to identify cardiovascular risks) there was no reported increase in cardiovascular adverse events.

**Figure 95**: Vascular and vaso-occlusive adverse events with incidence>.5% in any treatment group (all post-surgical studies combined)

| | placebo | celecoxib | diclofenac | opioids |
|---|---|---|---|---|
| Adverse event | | | | |
| No. treated | 488 | 716 | 230 | 375 |
| Myocardial, endocardial, pericardial, valve disorders | | | | |
| Any event | | 3 | 1 | 2 |
| Angina | | 2 | 1 | |
| Myoc. Isch. | | 1 | | |
| Coronary artery disorder | | | | 2 |
| Vascular (extracardiac) disorders | | | | |
| Any event | 2 | 1 | 3 | |
| Cerebrovascul. Disorder | 1 | | | |
| Phlebitis | | | 1 | |
| DVT | | 1 | 1 | |
| Vascular disorder | 1 | | | |

## Figure 96: Vascular and vaso-occlusive SAEs

**Table 15.k. Vascular and Vaso-occlusive Serious Adverse Events: All Studies**

| Study | Center-Patient | Age, Sex | Treatment | Event | DER No. | Attribution |
|---|---|---|---|---|---|---|
| 074 | SW0001-0359 | 85 M | Placebo | Cerebrovascular Disorder | 980529-CL192 | Uncertain |
| 075 | UK0003-0256 | 73 M | Celecoxib 200 mg | Thrombophlebitis Deep | 980828-CL352 | None |
| 075 | UK0004-0227 | 78 M | Celecoxib 200 mg | Myocardial Ischemia | 980616-CL088 | None |
| 075 | UK0007-0233 | 62 M | Diclofenac SR 75 mg | Thrombophlebitis Deep | 980604-CL230 | Uncertain |
| 082 | US0003-0009 | 64 M | Hydrocodone 10 mg/ Acetaminophen 1000 mg | Coronary Artery Disorder | 980327-CL864 | None |
| 082 | US0006-0066 | 66 M | Hydrocodone 10 mg/ Acetaminophen 1000 mg | Aortic Stenosis | 980617-CL182 | None |
| 082 | US0006-0066 | 66 M | Hydrocodone 10 mg/ Acetaminophen 1000 mg | Coronary Artery Disorder | 980617-CL182 | None |

Derived from Tables T13.1 to T13.7, and Appendices 2.1 and 2.3.

b. CNS and psychiatric events causing withdrawal

No CNS-, PNS-, or psychiatric-related serious adverse events occurred in any of the celecoxib pain studies.

**Figure 97**:Hematological serious adverse events

| Study | Center-Patient | Age, Sex | Treatment | Event | DER No. | Attribution |
|---|---|---|---|---|---|---|
| 074 | SP0001-0477 | 20 M | Diclofenac SR 75 mg | Hematoma NOS | 990115-CL611 | Uncertain |
| 074 | UK0004-0178 | 62 M | Placebo | Hematoma NOS | 980629-CL116 | None |
| 074 | SP0001-0476 | 42 M | Placebo | Hemorrhage NOS | 981209-CL999 | None |
| 075 | UK0007-0232 | 76 F | Celecoxib 200 mg | Embolism Pulmonary | 980828-CL360 | None |
| 083 | US0005-0091 | 51 F | Placebo | Embolism Pulmonary | 980812-CL198 | None |

Derived from Tables T13.1 to T13.7, and Appendices 2.1 and 2.3.

c. A single hematologic adverse event causing withdrawal occurred in the celecoxib pain studies; a patient who received a single dose of celecoxib 50 mg in a post-oral surgery trial experienced oral hemorrhage.

**Figure 98**:Renal serious adverse events

| Study | Center-Patient | Age, Sex | Treatment | Event | DER No. | Attribution |
|---|---|---|---|---|---|---|
| 074 | BE0010-0177 | 65 F | Diclofenac SR 75 mg | Hypertension | 980716-CL263 | Uncertain |
| 082 | NZ0007-0049 | 51 M | Hydrocodone 10 mg/ Acetaminophen 1000 mg | Renal Calculus | 980327-CL884 | None |

Derived from Tables T13.1 to T13.7, and Appendices 2.1 and 2.3.

d. No renal adverse events causing withdrawal occurred in patients on celecoxib in the pain studies.
No renal serious adverse events occurred related to celecoxib.

e.Hepatobiliary
No hepatobiliary adverse events causing withdrawal occurred in any of the celecoxib pain studies. There were no hepatobiliary disorders reported as serious adverse events during the celecoxib pain trials, although there was one individual with both an elevated SGPT and bilirubin.

**Figure 99**:Respiratory serious adverse events

| Study | Center-Patient | Age, Sex | Treatment | Event | DER No. | Attribution |
|---|---|---|---|---|---|---|
| 028 | US0009-0430 | 63 F | Celecoxib 100 mg | Pneumothorax | 971205-CL512 | None |
| 082 | US0002-0140 | 63 M | Hydrocodone 10 mg/ acetaminophen 1000 mg | Respiratory Disorder | 980619-CL843 | None |

Derived from Tables T13.1 to T13.7, and Appendices 2.1 and 2.3.

f. A single pulmonary/respiratory adverse event causing withdrawal occurred during the celecoxib pain studies. A patient who received celecoxib 200 mg in the European post-hernia repair pain study withdrew from the study due to dyspnea.

g. No endocrine/metabolic adverse events causing withdrawal occurred in the celecoxib pain studies. No endocrine/metabolic disorders were reported as serious adverse events in any of the celecoxib pain trials.

h. A total of four dermatologic adverse events causing withdrawal occurred during the celecoxib pain studies one patient who received celecoxib 200 mg in the musculoskeletal pain study experienced urticaria; one patient who received placebo in the musculoskeletal pain study developed rash maculopapular; and one patient each who received opioid comparator in the North American/New Zealand postsurgical pain studies experienced dermatitis and rash. No statistically significant differences were detected among the treatment groups for any of these events. No dermatologic serious adverse events were reported during the celecoxib pain studies.

i. Serious adverse events related to infections in all studies (Figure 100) Four events occurred in patients receiving celecoxib. Patient US0008-0455, who was randomized to receive celecoxib 200 mg in a North American/New Zealand postsurgical pain study, developed infection four days after initial dosing. Patient SP0003-0002, who was assigned to receive celecoxib 200 mg in the European post-hernia repair pain study, experienced infection after a single dose of study medication. Patient US0001-0149, who was randomized to receive celecoxib 200 mg in a North American/New Zealand postsurgical pain study, developed osteomyelitis two days after the last dose of study medication. Patient UK0004-0227, who was randomized to receive celecoxib 200 mg in the European post-hip replacement pain study, developed cellulitis twenty-eight days after the final dose of study medication. Two adverse events related to postsurgical infection resulted study withdrawal during the

celecoxib pain studies: infection and fever; neither event occurred among patients who received celecoxib.

Figure 100: Serious adverse events related to infections

| Study | Center-Patient | Age, Sex | Treatment | Event | DER No. | Attribution |
|---|---|---|---|---|---|---|
| 028 | US0004-0148 | 82 M | Propoxyphene napsylate 100 mg/ acetaminophen 650 mg | Cellulitis | 980112-CL829 | None |
| 028 | US0004-0329 | 75 F | Placebo | Healing impaired | 971007-CL822 | None |
| 029 | NZ0007-0107 | 21 M | Propoxyphene napsylate 100 mg/ acetaminophen 650 mg | Infection | 971205-CL531 | None |
| 029 | US0006-0413 | 43 F | Placebo | Abscess | 971109-CL730 | None |
| 029 | US0008-0455 | 68 F | Celecoxib 200 mg | Infection | 971205-CL529 | None |
| 074 | DE0001-0381 | 76 M | Placebo | Fever | 990219-CL511 | None |
| 074 | SP0003-0002 | 76 M | Celecoxib 200 mg | Infection | 980408-CL205 | None |
| 074 | UK0003-0211 | 68 M | Placebo | Fever | 980828-CL361 | None |
| 075 | UK0004-0227 | 78 M | Celecoxib 200 mg | Cellulitis | 980616-CL088 | None |
| 082 | US0002-0048 | 71 F | Hydrocodone 10 mg/acetaminophen 1000 mg | Cellulitis | 980717-CL576 | None |
| 083 | US0001-0152 | 38 F | Hydrocodone 10 mg/acetaminophen 1000 mg | Fever | 980812-CL205 | None |
| 086 | US0001-0149 | 88 F | Celecoxib 200 mg | Osteomyelitis | 980410-CL827 | None |
| 086 | US0008-0165 | 76 F | Hydrocodone 10 mg/acetaminophen 1000 mg | Abnormal serous wound drainage | 980429-CL122 | None |

Derived from Tables T13.1 to T13.7, and Appendices 2.1 and 2.3.

i. Two musculoskeletal adverse events causing withdrawal were reported in the celecoxib pain studies: one patient who received celecoxib 200 mg in a North American/New Zealand postsurgical pain study experienced arthralgia, and one patient who received placebo in the musculoskeletal pain study developed arthrosis. No musculoskeletal serious adverse events occurred during the celecoxib pain studies.

j.High risk populations: no subgroup analyses were performed by age for the oral surgery and dysmenorrhea studies (most individuals were <44 years of age). For the musculoskeletal studies there were too few patients to perform an analysis. For the post surgical studies the only differences between the <65 and >65 populations were for hypertonia and hypoesthesia (see figure).

**Figure 101: Risk differences between age groups**

| | <65 Years | | | ≥65 Years | | |
|---|---|---|---|---|---|---|
| | Celecoxib† | Placebo | RD | Celecoxib† | Placebo | RD |
| No. Treated | 358 | 296 | | 135 | 79 | |
| Hypertonia | 1.1 | 0.7 | 0.4 | 0.0 | 3.8 | -3.8 |
| Hypoesthesia | 0.8 | 0.0 | 0.8 | 0.0 | 1.3 | -1.3 |

Derived from Table T12.1. Table includes events in Studies 028, 029, 080, 082, 083, 085, and 086 for which the difference in RDs was statistically significant at p<0.05. Data represent % patients unless otherwise indicated.

† Includes celecoxib 200 mg per day, 2 doses (100 mg or 200 mg) per day PRN, and 200 mg BID or TID PRN treatment groups.

5. drug-drug and other interactions

No specific discussion of drug-drug interactions was presented in this submission. However, information is available from the original NDA submission and is presented in the label for celecoxib. Management of these interactions should not pose a significant problem, as for the most part these are recognized as potential problems associated with the use of other NSAID's in general. Celecoxib metabolism is mediated by cytochrome P450 2C9 in the liver. Therefore, it is recommended that coadministration of celecoxib with drugs that are known to inhibit 2C9 should be undertaken with caution. The interaction with ACE inhibitors should be considered as is the case for other NSAID's. NSAID's have

been shown to reduce the natriuretic effect of furosemide and thiazides in some patients. Celecoxib may be used with aspirin although concomitant use appears to result in an increased rate of GI ulcerations and other complications compared to celecoxib alone. However, celecoxib does not appear to alter the anticoagulant effect of warfarin as determined by prothrombin time. Again, these problems are in general well recognized ones associated with NSAID use and the medical community is likely to be well aware of these issues. Two cases of special consideration should be addressed. Addition of celecoxib leads to an increase in mean steady state plasma levels of lithium by 17%. Administration of celecoxib and fluconazole leads to an increase of celecoxib levels by 2-fold. These drug interactions are already addressed in the label.

6. withdrawal phenomena/abuse potential

Celecoxib is a non-narcotic analgesic agent with no attributes that suggest a potential for drug abuse. There are no reports of dependence or withdrawal effects.

7. human reproduction data

Pregnant women were excluded from these trials. Two unintended pregnancies occurred during these studies but neither patient received celecoxib.

8. post marketing data

Serious adverse events were reported in postmarketing surveillance. The most common serious adverse events were GI in nature. A qualitative analysis shows that of the 30 fatal GI events most occurred in elderly individuals with co-morbidities. Rare serious events not previously found in the label are in Figure 102.

**Figure 102**:Rare serious adverse events

| Event | Reporting Rate |
|---|---|
| **Cardiovascular** | |
| Vasculitis | 8 (0.4) |
| **Liver and biliary** | |
| Hepatitis | 9 (0.5) |
| Jaundice | 26 (1.5) |
| Hepatic failure | 8 (0.4) |
| **Hemic and lymphatic** | |
| Agranulocytosis | 3 (0.2) |
| Aplastic anemia | 6 (0.3) |
| Pancytopenia | 7 (0.4) |
| Leukopenia | 16 (0.9) |
| **Metabolic** | |
| Hypoglycemia | 7 (0.4) |
| **Renal** | |
| Interstitial nephritis | 4 (0.2) |
| **Skin** | |
| Erythema multiforme | 6 (0.3) |
| Exfoliative dermatitis | 3 (0.2) |
| Stevens-Johnson syndrome | 6 (0.3) |
| Epidermal necrolysis | 2 (0.1) |
| **General** | |
| Anaphylactoid reaction | 19 (1.1) |
| Angioedema | 34 (1.9) |

All numbers represent number of patients (number per 100,000 patient-years).

## VIII. Dosing, Regimen, and Administration Issues

The following tables demonstrate that celecoxib 400 mg was the maximally efficacious dose. Celecoxib 400 mg provided the greatest percent of patients with onset of analgesia (Figure 103), the fastest median time to onset of analgesia, the most improved time weighted summed measures of efficacy (Figure 104), and the longest time to rescue medication and lowest percent of patients who took rescue medication (Figure 105).

## Figure 103: Percent of patients with onset of analgesia and time to onset of analgesia

| Treatment Group | Study 025 | | Study 027 | | Study 070 | |
|---|---|---|---|---|---|---|
| | Median Time to Onset of Analgesia (hr:min) | Percent of Patients with Onset of Analgesia | Median Time to Onset of Analgesia (hr:min) | Percent of Patients with Onset of Analgesia | Median Time to Onset of Analgesia (hr:min) | Percent of Patients with Onset of Analgesia |
| Celecoxib 400 mg | - | - | - | - | 00:54 (AB) | 60% |
| Celecoxib 200 mg | 01:15 (B) | 54% | 00:36 (B) | 71% | 01:00 (B) | 54% |
| Celecoxib 100 mg | - | - | 00:57 (C) | 53% | 00:54 (AB) | 54% |
| Celecoxib 50 mg | >24:00 (B) | 46% | - | - | >24:00 (B) | 49% |
| Placebo | >24:00 (C) | 18% | >24:00 (D) | 24% | >24:00 (C) | 12% |

Source: Appendix 2.1.2.

## Figure 104: Time weighted summed measures of efficacy at specific doses

| Treatment Group | Study 025 | | Study 027 | | Study 070 | |
|---|---|---|---|---|---|---|
| | SPID(8) | TOTPAR(8) | SPID(8) | TOTPAR(8) | SPID(8) | TOTPAR(8) |
| Celecoxib 400 mg | - | - | - | - | 5.50 (AB) | 13.71 (AB) |
| Celecoxib 200 mg | 3.99 (B) | 12.14 (A) | 6.13 (A) | 14.62 (A) | 5.75 (B) | 10.82 (BC) |
| Celecoxib 100 mg | - | - | 3.84 (B) | 11.15 (B) | 5.28 (B) | 10.81 (BC) |
| Celecoxib 50 mg | 3.00 (B) | 8.38 (B) | - | - | 2.54 (B) | 7.79 (C) |
| Placebo | -0.51 (D) | 4.01 (C) | -1.20 (C) | 4.54 (C) | -0 33 (C) | 2.89 (D) |

Source: Appendix 2.1.6.

## Figure 105: Time to rescue and percent who took rescue medication for specific doses

| Treatment Group | Study 025 | | Study 027 | | Study 070 | |
|---|---|---|---|---|---|---|
| | Median Time to Rescue Medication (hr:min) | Percent of Patients Who Took Rescue Medication | Median Time to Rescue Medication (hr:min) | Percent of Patients Who Took Rescue Medication | Median Time to Rescue Medication (hr:min) | Percent of Patients Who Took Rescue Medication |
| | | 24 hr | | 24 hr | | 24 hr |
| Celecoxib 400 mg | - | - | - | - | 08:13 (AB) | 63% |
| Celecoxib 200 mg | 03:05 (AB) | 74% | 10:02 (AB) | 52% | 04:15 (AB) | 76% |
| Celecoxib 100 mg | - | - | 04:17 (B) | 69% | 02:36 (AB) | 80% |
| Celecoxib 50 mg | 01:48 (AB) | 86% | - | - | 01:41 (B) | 91% |
| Placebo | 01:17 (C) | 92% | 01:20 (C) | 84% | 01:06 (C) | 96% |

Source: Appendix 2.1.7.
8-hour values estimated from Kaplan-Meier plots.

Additional data supporting the analgesic efficacy of celecoxib 400 mg were obtained from the 2 dysmenorrhea studies. Figure 106 provides data supporting the efficacy of an additional dose of celecoxib 200 mg in the first 24 hours. *A second dose of celecoxib allowed an additional 15-24% of patients to complete the first 24 hours of each treatment period.*

**Figure 106: Efficacy of additional dose of celecoxib**

| Study Day | Placebo | | Celecoxib 400 mg/200 mg PRN | | Naproxen Sodium 550 mg PRN | |
|---|---|---|---|---|---|---|
| | 129 | 130 | 129 | 130 | 129 | 130 |
| 24-hour Analgesia After One Dose (%) | 34% | 49% | 49% | 54% | 48% | 69% |
| 24-hour Analgesia After Two Doses (%) | 12% | 9% | 24% | 15% | 26% | 11% |
| Rescue Within 24 Hours | 52% | 42% | 26% | 31% | 23% | 18% |

Source: Appendix 5.1.2.

Furthermore, studies 085 and 086 provide data to show that for pain control after the first day, 53% of patients of patients took 2 or less doses of celecoxib to maintain analgesia (see day 2, for example) (figure 107).

**Figure 107**: Number of doses needed each day to maintain analgesia after day 1

| Study Day | Celecoxib 200 mg PRN | Hydrocodone 10 mg/ Acetaminophen 1000 mg PRN |
|---|---|---|
| **Day 2** | | |
| 0 dose | 12% | 7% |
| 1 dose | 13% | 9% |
| 2 doses | 28% | 26% |
| 3 doses | 39% | 46% |
| Rescue | 9% | 13% |
| **Day 3** | | |
| 0 dose | 23% | 10% |
| 1 dose | 16% | 15% |
| 2 doses | 30% | 24% |
| 3 doses | 29% | 45% |
| Rescue | 3% | 6% |
| **Day 4** | | |
| 0 dose | 30% | 17% |
| 1 dose | 15% | 17% |
| 2 doses | 27% | 25% |
| 3 doses | 26% | 39% |
| Rescue | 1% | 2% |
| **Day 5** | | |
| 0 dose | 41% | 20% |
| 1 dose | 18% | 20% |
| 2 doses | 14% | 29% |
| 3 doses | 27% | 31% |

Source: Appendix 6.1.4.3.

In total, the data supports the dosing regimen recommended by the sponsor. A single initial dose of celecoxib 400 mg followed by 200 mg daily with an additional 200 mg each day as needed should provide the needed analgesia in the acute setting.

## IX. Use in Special Populations

### A. Gender

With respect to gender the pivotal studies involving males and females include the post oral surgery pain (025, 027,070) studies and the postsurgical pain studies (082,083,085,086). In single doses celecoxib at doses of 200 mg or 400 mg showed no significant differences in analgesic efficacy. The studies for dysmenorrhea involved only women.

### B. Age, Race, or Ethnicity

With respect to age, single doses of celecoxib 200 mg showed consistent analgesic efficacy regardless of age greater or less than 65 in post surgical pain studies (082,083,085,086). There were no patients greater than 65 in the dysmenorrhea and post oral surgery studies. In the label for celecoxib, more than 3300 patients ages 65-74 and about 1300 over 75 took this drug. The incidence of adverse events tended to be higher in elderly patients no substantial differences in safety and effectiveness were observed between these patients and younger subjects. With respect to ethnic origin, single doses of celecoxib 200 mg and 400 mg showed no important differences in analgesic efficacy among patients of different ethnic origins. Although significant differences were present between the Black and Caucasian/Hispanic groups this appeared to be due to the small number of Blacks in the studies.

### C. Pediatric Studies

There were no pediatric patients entered in these studies. [

]

### D. Other populations

Celecoxib is already approved for use. The label states that when used in patients with moderate hepatic insufficiency the dose should be reduced by approximately 50%. Celecoxib is not recommended for treatment in patients with advanced kidney disease. There are no studies in pregnant women. The present studies do not address further any of these issues.

## X. Conclusions and Recommendations

### A. Conclusions

1) The sponsor has demonstrated the efficacy of celecoixb for the treatment of acute pain and dysmenorrhea.
2) The sponsor has not demonstrated superiority of celecoxib to the standards of care used as comparators. In almost all cases celecoxib was found to be comparable to or less efficacious than the positive comparators evaluated in these studies in terms of onset or magnitude of pain relief and duration. For example, in the dysmenorrhea studies naproxen was statistically superior to celecoxib for measures such as SPID and TOTPAR.
3) The NSAID comparators ibuprofen 400mg and naproxen sodium 550mg used in the post-surgical studies demonstrated a more rapid onset of analgesia and a significantly greater peak response than celecoxib beginning at 30-45 minutes post dose.
4) No studies were submitted comparing celecoxib to other Cox-2 selective agents.
5) In terms of risk and safety profile, celecoxib has not been demonstrated to be superior to the comparators used in these studies, although they were not powered to examine these issues. In a separate study powered to examine safety of chronic use, celecoxib was not proven to be superior to the 2 comparators examined.

There may be some benefit to using celecoxib in the post-operative setting where narcotic analgesia may cause unwanted sedation or GI problems. However, celecoxib was not as efficacious as narcotics in the treatment of severe post-operative pain. In this setting, celecoxib may best used as adjunctive therapy.

Future studies examining therapy for acute pain need to more carefully address the issue of the multiple dose period. Current pain models and study designs may be inadequate to robustly assess optimal dose intervals based on multidose efficacy. Current study designs do not appear to provide sufficient numbers of patients for dosing beyond the first day. Either new models need to be incorporated in these studies or sufficient numbers of patients need to be entered to account for the significant patient dropout seen in the present models used (individuals entering the multi-dose phase can be randomized at the time they enter this phase). In the absence of multidose assessment, conclusions about dosing intervals may be drawn from time to rescue medication, limited multidose efficacy data, PK studies, and pain curves comparing active treatment and placebo.

Finally, pain studies need to be appropriately powered to identify statistically meaningful differences that are also clinically relevant. Incorporation of large numbers of patients may identify statistical differences that are not clinically meaningful.

## B. Recommendations

The sponsor has demonstrated that celecoxib provides benefit to those individuals with acute pain such as may occur post-surgically or associated with dysmenorrhea. The common side effects and risks are well recognized. Based on the benefits and risks provided by celecoxib and from a clinical perspective, celecoxib is approvable for the indications of acute pain and dysmenorrhea. The initial dose of 400 mg followed by 200 mg daily appears to be efficacious.

Celecoxib appears most efficacious for the treatment of acute pain following dental surgery or from dysmenorrhea, but results were less robust for the treatment of the level of acute pain that typically follows major surgery such as a hip or knee replacement. In these cases the clinician may still want to consider the use of a narcotic analgesic to insure the most efficient treatment of pain.

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