Table 3
Summary for Clinically Significant Hemoglobin (Hgb) Decreases: All Treated Patients Taking Aspirin

	Celecoxib 400 mg BID N (%)	Diclofenac 75 BID N (%)	Ibuprofen 800 mg TID N (%)	------- p-value ------- Celecoxib vs Diclofenac (%)	------- p-value ------- Celecoxib vs Ibuprofen
Number of Patients	882	445	412		
Hgb decrease >2 g/dL at 1 or more visits	34 (3.9)	29 (6.5)	29 (7.0)	0.040*	0.018*
Hgb decrease >2 g/dL at 2 consecutive visits	7 (0.8)	9 (2.0)	10 (2.4)	0.064+	0.032*

Note: P-value from Fisher's exact test.

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Attachment 2
Data submitted 4/23/02 used to support labeling changes

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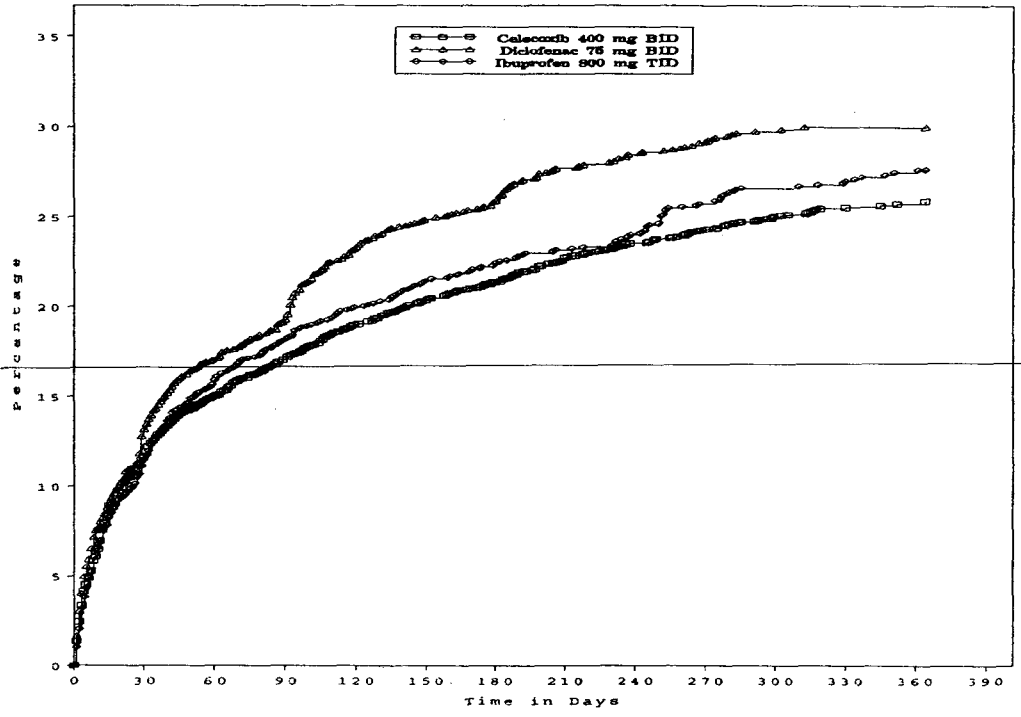
Table T17

Kaplan-Meier Plot of Time to Any Adverse Events Causing Withdrawal: Entire Study Period



Event Rates (%)

Time Point	Celecoxib 400 mg BID # at Risk on this day	Celecoxib 400 mg BID K-M Cum. Rate	Diclofenac 75 mg BID # at Risk on this day	Diclofenac 75 mg BID K-M Cum. Rate	Ibuprofen 800 mg TID # at Risk on this day	Ibuprofen 800 mg TID K-M Cum. Rate
TREATED PATIENTS	3987		1996		1985	
Week 1 (Day 7)	3739	5.29	1851	6.56	1851	5.24
Week 4 (Day 28)	3367	11.24	1690	11.82	1660	10.68
Week 13 (Day 91)	2771	17.22	1362	19.57	1274	18.27
Week 26 (Day 182)	2298	21.44	1102	26.17	1019	22.52
Week 39 (Day 273)	1992	24.31	959	29.33	872	25.72
Week 52 (Day 364)	532	25.88	54	29.99	447	27.64

Log-Rank test p-values

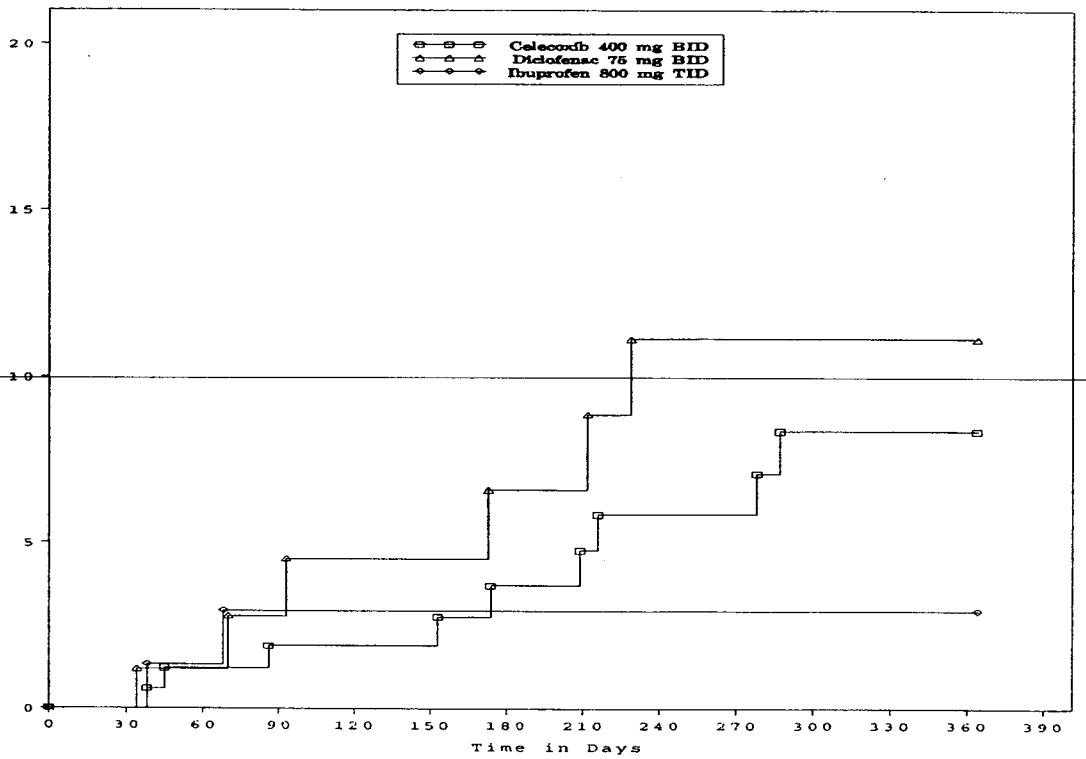
Celecoxib vs Diclofenac	<0.001***
Celecoxib vs Ibuprofen	0.314
Celecoxib vs NSAIDs	0.006**

Note: Event rates are based on Kaplan-Meier estimates.

***, **, *, + Statistically significant at p=0.001, 0.01, 0.05, and 0.10, respectively.

Table T18.1

Kaplan – Meier Plot of Time to Any Serious Cardiovascular AEs: Entire Study Period
Patients with History of MI or Angina Pectoris



Event Rates (%)

Time Point	Celecoxib 400 mg BID # at Risk on this day	Celecoxib 400 mg BID K-M Cum. Rate	Diclofenac 75 mg BID # at Risk on this day	Diclofenac 75 mg BID K-M Cum. Rate	Ibuprofen 800 mg TID # at Risk on this day	Ibuprofen 800 mg TID K-M Cum. Rate
TREATED PATIENTS	229		99		96	
Week 1 (Day 7)	220	0.00	95	0.00	94	0.00
Week 13 (Day 91)	140	1.89	58	2.78	58	2.95
Week 26 (Day 182)	99	3.71	44	6.60	47	2.95
Week 39 (Day 273)	82	5.86	37	11.15	39	2.95
Week 52 (Day 364)	25	8.37	5	11.15	19	2.95

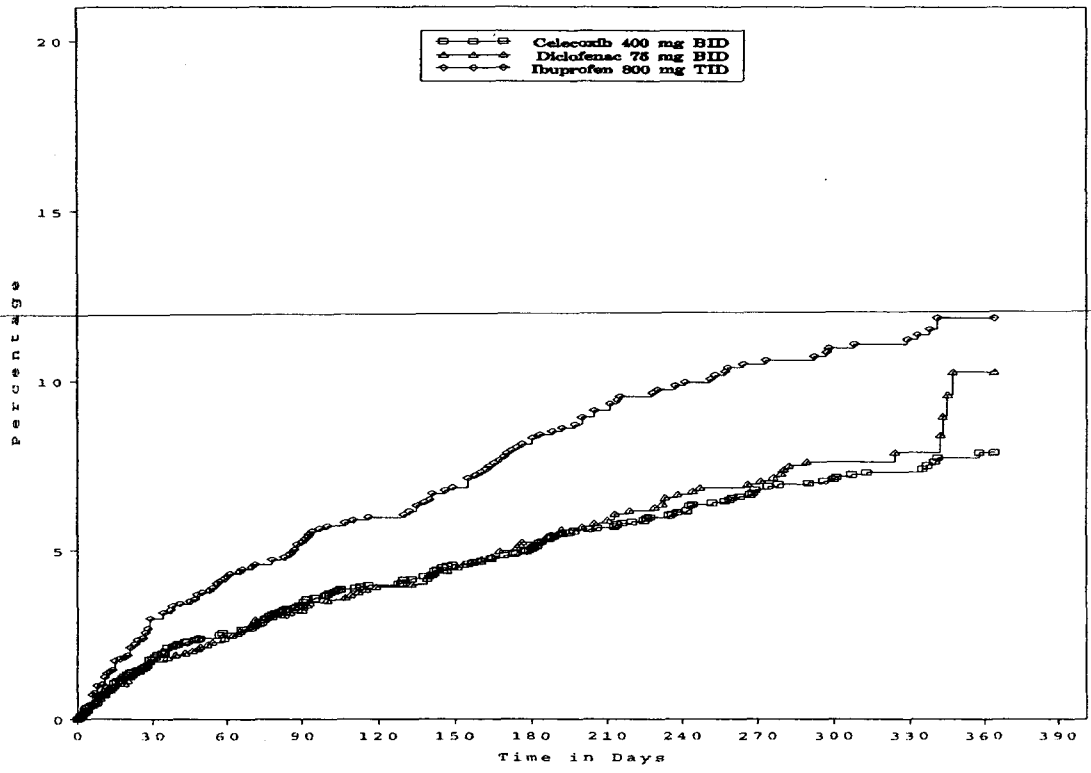
Log-Rank test p-values

Celecoxib vs Diclofenac	0.436
Celecoxib vs Ibuprofen	0.354
Celecoxib vs NSAIDs	0.988

Note: Event rates are based on Kaplan-Meier estimates.
Cardiovascular AEs includes MI, unstable angina, cerebrovascular disorder, thrombophlebitis deep, thrombophlebitis leg deep, peripheral gangrene, peripheral ischemia and embolism pulmonary.

Table T23

Kaplan – Meier Plot of Time to Any Edema Peripheral or Hypertension AEs: Entire Study Period



Event Rates (%)

Time Point	Celecoxib 400 mg BID # at Risk on this day	Celecoxib 400 mg BID K-M Cum. Rate	Diclofenac 75 mg BID # at Risk on this day	Diclofenac 75 mg BID K-M Cum. Rate	Ibuprofen 800 mg TID # at Risk on this day	Ibuprofen 800 mg TID K-M Cum. Rate
TREATED PATIENTS	3987		1996		1985	
Week 1 (Day 7)	3828	0.46	1911	0.51	1894	0.77
Week 4 (Day 28)	3442	1.60	1723	1.55	1689	2.70
Week 13 (Day 91)	2768	3.49	1359	3.24	1242	5.33
Week 26 (Day 182)	2255	5.14	1084	5.26	965	8.32
Week 39 (Day 273)	1914	6.79	917	7.05	810	10.61
Week 52 (Day 364)	509	7.90	50	10.28	408	11.86

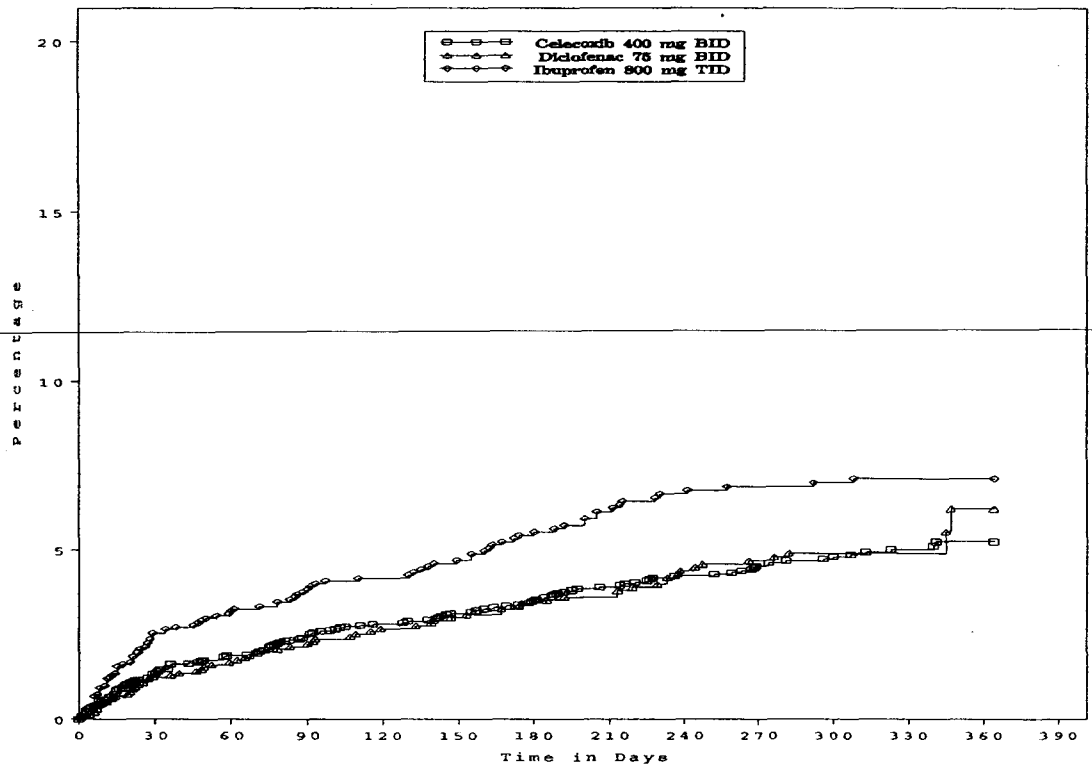
Log-Rank test p-values

Celecoxib vs Diclofenac	0.527
Celecoxib vs Ibuprofen	<0.001***
Celecoxib vs NSAIDs	0.003**

Note: Event rates are based on Kaplan-Meier estimates.
***, **, *, + Statistically significant at p=0.001, 0.01, 0.05, and 0.10, respectively.

Table T24

Kaplan-Meier Plot of Time to Any Edema Peripheral AEs: Entire Study Period



Event Rates (%)

Time Point	Celecoxib 400 mg BID # at Risk on this day	Celecoxib 400 mg BID K-M Cum. Rate	Diclofenac 75 mg BID # at Risk on this day	Diclofenac 75 mg BID K-M Cum. Rate	Ibuprofen 800 mg TID # at Risk on this day	Ibuprofen 800 mg TID K-M Cum. Rate
TREATED PATIENTS	3987		1996		1985	
Week 1 (Day 7)	3830	0.41	1914	0.31	1895	0.72
Week 4 (Day 28)	3453	1.22	1727	1.19	1693	2.37
Week 13 (Day 91)	2787	2.54	1368	2.24	1257	3.94
Week 26 (Day 182)	2276	3.57	1097	3.45	991	5.54
Week 39 (Day 273)	1946	4.54	934	4.69	838	6.88
Week 52 (Day 364)	519	5.26	51	6.23	425	7.12

Log-Rank test p-values

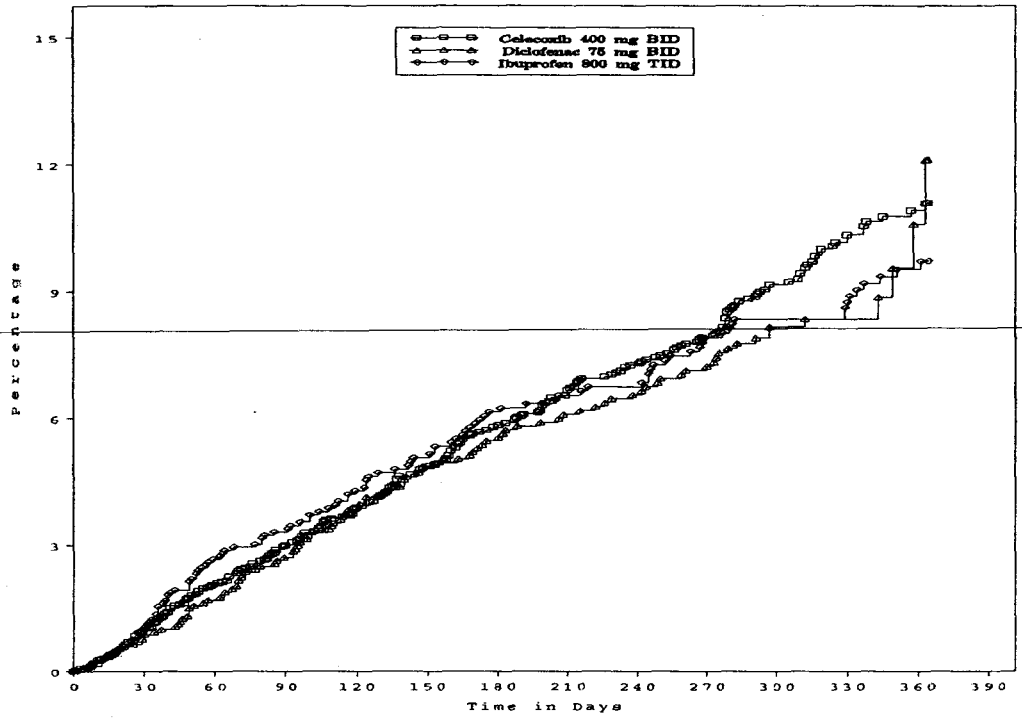
Celecoxib vs Diclofenac	0.968
Celecoxib vs Ibuprofen	0.003**
Celecoxib vs NSAIDs	0.065+

Note: Event rates are based on Kaplan-Meier estimates.

***, **, *, + Statistically significant at p=0.001, 0.01, 0.05, and 0.10, respectively.

Table T16

Kaplan-Meier Plot of Time to Any Serious Adverse Events: Entire Study Period



Event Rates (%)

Time Point	Celecoxib 400 mg BID # at Risk on this day	Celecoxib 400 mg BID K-M Cum. Rate	Diclofenac 75 mg BID # at Risk on this day	Diclofenac 75 mg BID K-M Cum. Rate	Ibuprofen 800 mg TID # at Risk on this day	Ibuprofen 800 mg TID K-M Cum. Rate
TREATED PATIENTS	3987		1936		1985	
Week 1 (Day 7)	3844	0.10	1917	0.21	1908	0.10
Week 4 (Day 28)	3470	0.93	1745	0.64	1717	0.93
Week 13 (Day 91)	2799	3.01	1378	2.71	1279	3.39
Week 26 (Day 182)	2270	5.84	1092	5.63	1003	6.24
Week 39 (Day 273)	1931	7.96	928	7.33	854	7.90
Week 52 (Day 364)	501	11.10	52	12.12	427	9.73

Log-Rank test p-values

Celecoxib vs Diclofenac	0.307
Celecoxib vs Ibuprofen	0.461
Celecoxib vs NSAIDs	0.261

Note: Event rates are based on Kaplan-Meier estimates.

Table T1
Incidence of Serious Cardiovascular Adverse Events per 100 Patient-Years: Entire Study Period

	Celecoxib 400 mg BID N (%)	Diclofenac 75 mg BID N (%)	Ibuprofen 800 mg TID N (%)
ALL TREATED PATIENTS	3987	1996	1985
PATIENT-YEARS	2320.4	1080.5	1122.5
ANY EVENT	44 (1.9)	20 (1.9)	19 (1.7)
Myocardial Infrarction	19 (0.8)	4 (0.4)	9 (0.8)
Unstable Angina	8 (0.3)	4 (0.4)	0 (0.0)
Cerebrovascular Disorder	4 (0.2)	6 (0.6)	6 (0.5)
DVT	8 (0.3)	6 (0.6)	1 (<0.1)
Peripheral Gangrene/Ischemia	3 (0.1)	0 (0.0)	1 (<0.1)
Embolism Pulmonary	4 (0.2)	1 (<0.1)	2 (0.2)

Note: If a patient had more than one adverse event within a body system, that patient is counted once in the overall incidence for that body system.

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Table T2
Incidence of Serious Cardiovascular Adverse Events per 100 Patient-Years: Entire Study Period

Patients not Taking Aspirin

	Celecoxib 400 mg BID N (%)	Diclofenac 75 mg BID N (%)	Ibuprofen 800 mg TID N (%)
ALL TREATED PATIENTS	3105	1551	1573
PATIENT-YEARS	1803.5	841.2	873.8
ANY EVENT	20 (1.1)	10 (1.2)	7 (0.8)
Myocardial Infrarction	6 (0.3)	2 (0.2)	2 (0.2)
Unstable Angina	2 (0.1)	0 (0.0)	0 (0.0)
Cerebrovascular Disorder	2 (0.1)	4 (0.5)	2 (0.2)
DVT	8 (0.4)	4 (0.5)	0 (0.0)
Peripheral Gangrene/Ischemia	1 (<0.1)	0 (0.0)	1 (0.1)
Embolism Pulmonary	3 (0.2)	1 (0.1)	2 (0.2)

Note: If a patient had more than one adverse event within a body system, that patient is counted once in the overall incidence for that body system.

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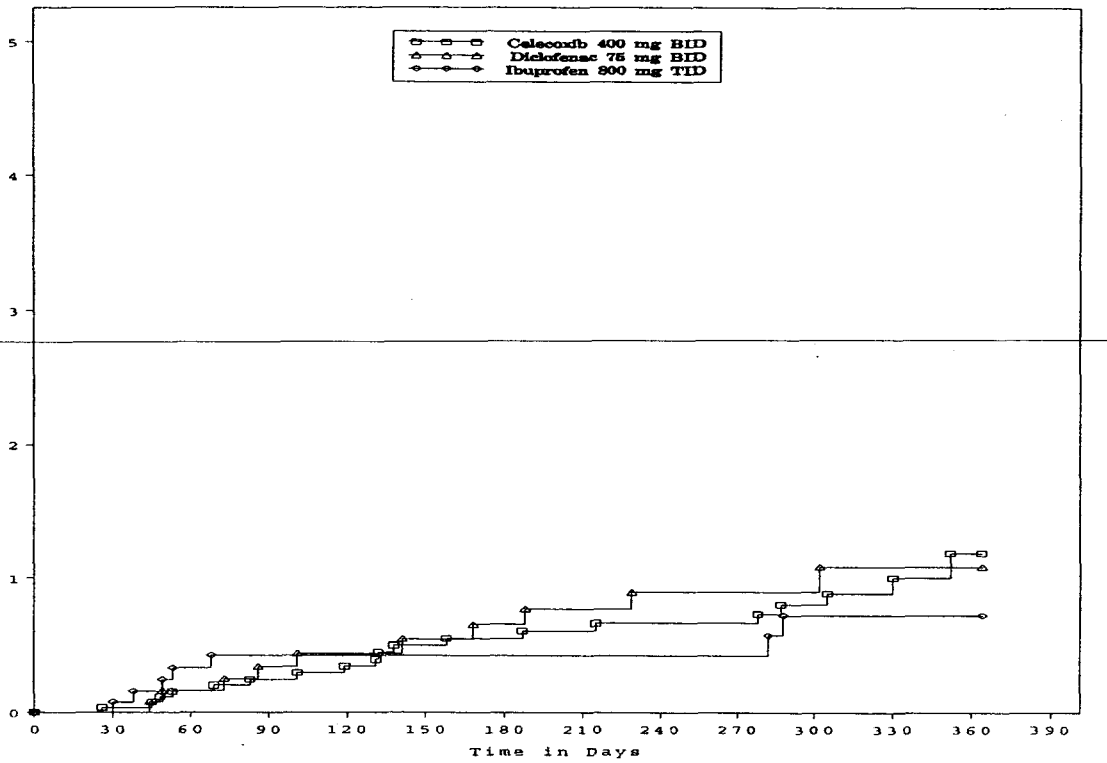
Figure F6.2

Kaplan – Meier Plot of Time to Any Serious Cardiovascular AEs: Entire Study Period
Patients not Taking Aspirin



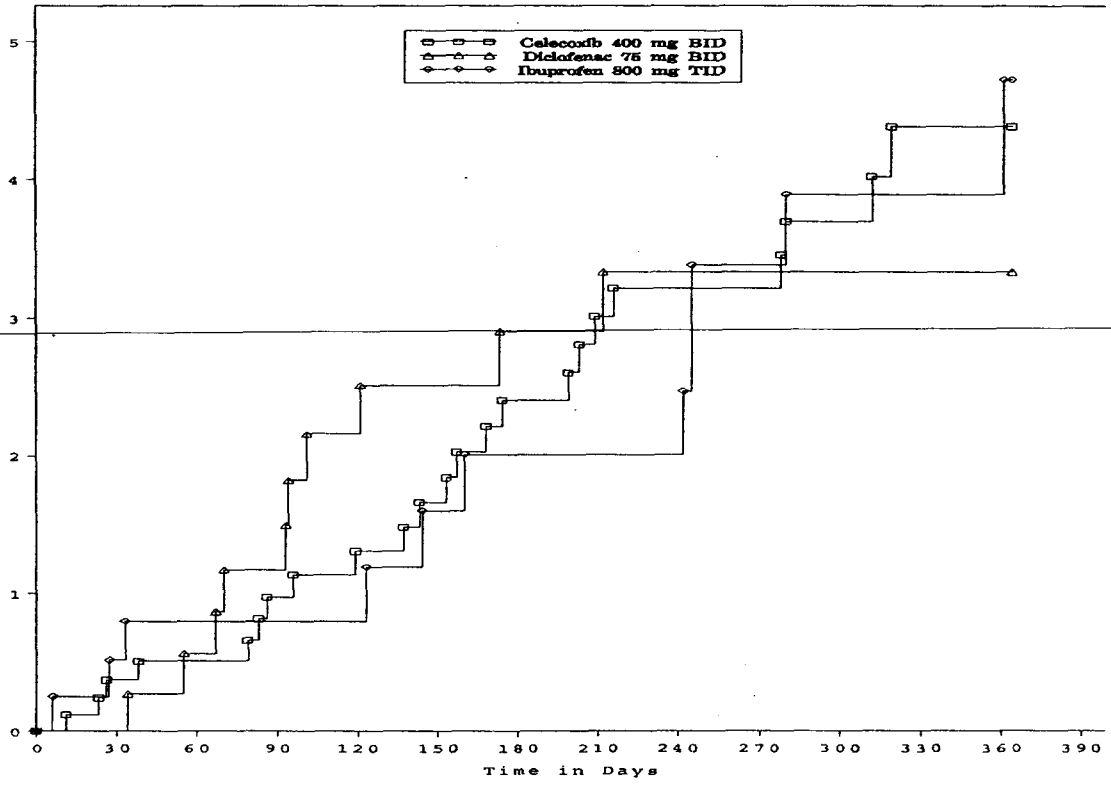
Event Rates (%)

Time Point	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
TREATED PATIENTS	3105	1551	1573
Week 1 (Day 7)	0.00	0.00	0.00
Week 4 (Day 28)	0.04	0.00	0.00
Week 13 (Day 91)	0.25	0.34	0.42
Week 26 (Day 182)	0.55	0.66	0.42
Week 39 (Day 273)	0.67	0.90	0.42
Week 52 (Day 364)	1.19	1.09	0.73
Log-Rank test p-values			
Celecoxib vs Diclofenac	0.738		
Celecoxib vs Ibuprofen	0.533		
Celecoxib vs NSAIDs	0.857		

Note: Event rates are based on Kaplan-Meier estimates.

Figure F6.3

Kaplan–Meier Plot of Time to Any Serious Cardiovascular AEs: Entire Study Period
Patients Taking Aspirin



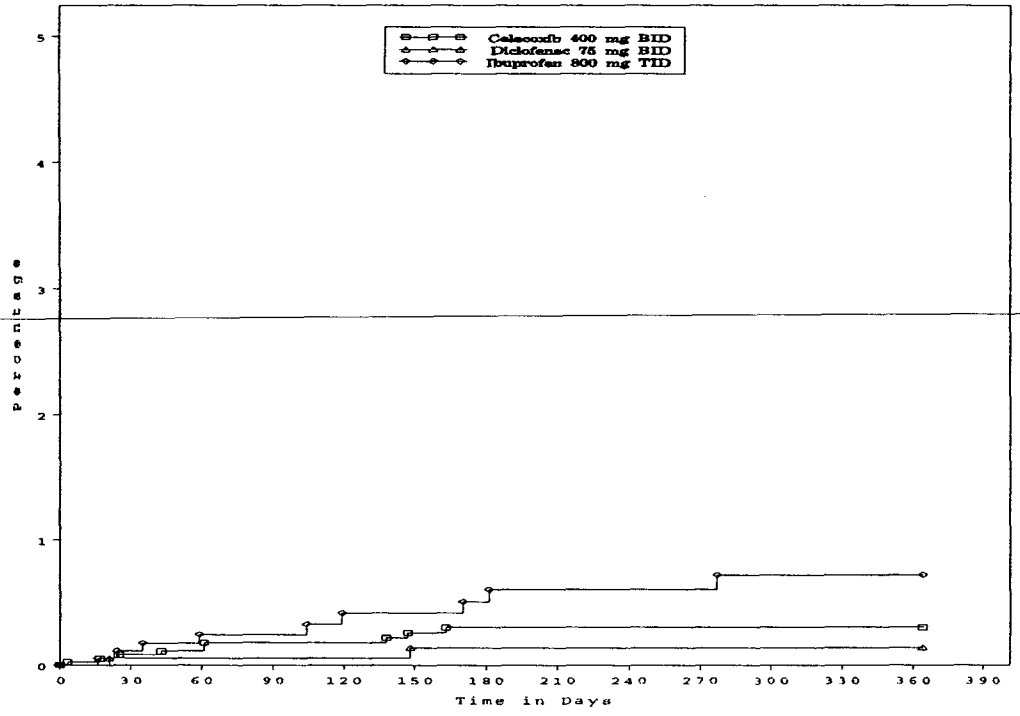
Event Rates (%)

Time Point	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
TREATED PATIENTS	882	445	412
Week 1 (Day 7)	0.00	0.00	0.25
Week 4 (Day 28)	0.37	0.00	0.51
Week 13 (Day 91)	0.97	1.17	0.80
Week 26 (Day 182)	2.40	2.90	2.01
Week 39 (Day 273)	3.22	3.33	3.38
Week 52 (Day 364)	4.38	3.33	4.72
Log-Rank test p-values			
Celecoxib vs Diclofenac	0.808		
Celecoxib vs Ibuprofen	0.992		
Celecoxib vs NSAIDs	0.914		

Note: Event rates are based on Kaplan-Meier estimates.

Figure F7.1

Kaplan – Meier Plot of Time to Any Serious Cardiac Failure: Entire Study Period



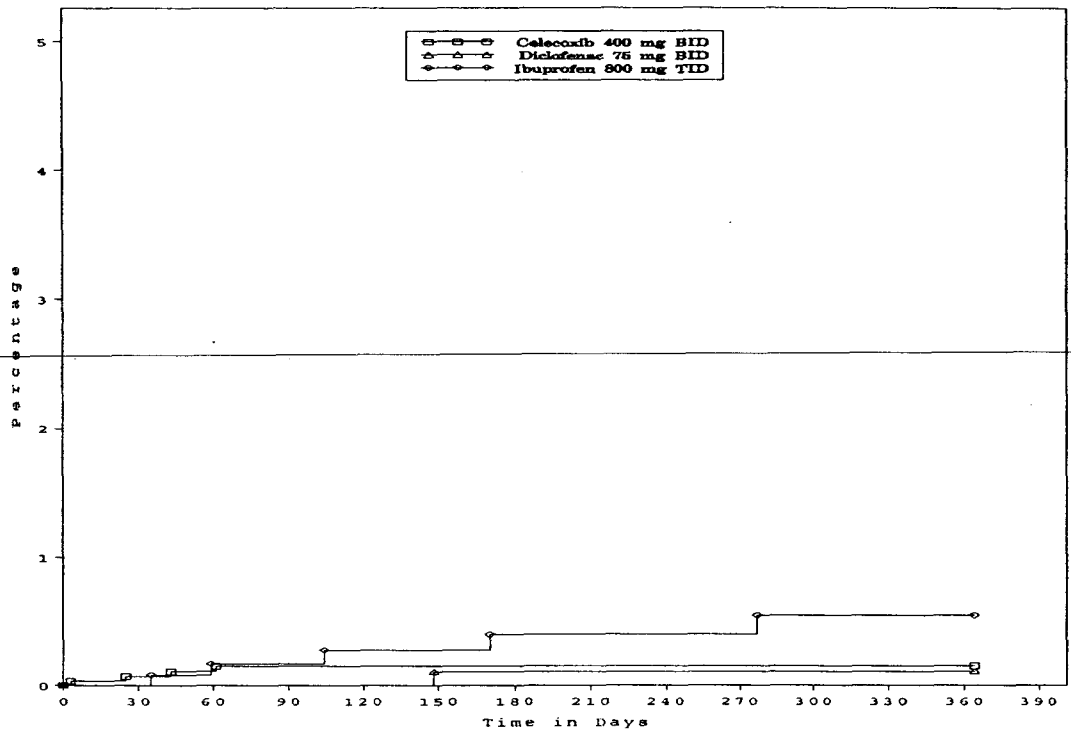
Event Rates (%)

Time Point	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
TREATED PATIENTS	3987	1996	1985
Week 1 (Day 7)	0.03	0.00	0.00
Week 4 (Day 28)	0.08	0.06	0.11
Week 13 (Day 91)	0.18	0.06	0.24
Week 26 (Day 182)	0.30	0.14	0.69
Week 52 (Day 364)	0.30	0.14	0.72
Log-Rank test p-values			
Celecoxib vs Diclofenac	0.295		
Celecoxib vs Ibuprofen	0.100+		
Celecoxib vs NSAIDs	0.593		

Note: Event rates are based on Kaplan-Meier estimates.
***, **, *, + Statistically significant at p=0.001, 0.01, 0.05, and 0.10, respectively.

Figure F7.2

Kaplan – Meier Plot of Time to Any Serious Cardiac Failure: Entire Study Period
Patients not Taking Aspirin



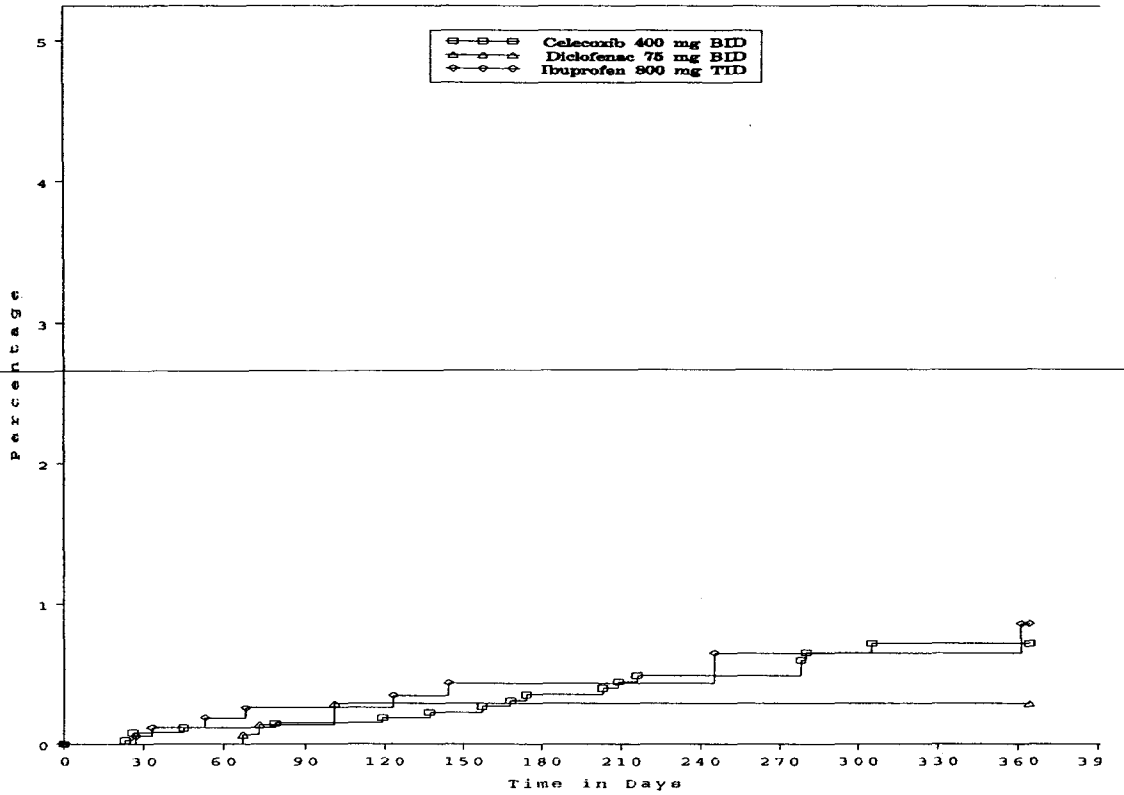
Event Rates (%)

Time Point	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
TREATED PATIENTS	3105	1551	1573
Week 1 (Day 7)	0.03	0.00	0.00
Week 4 (Day 28)	0.07	0.00	0.00
Week 13 (Day 91)	0.15	0.00	0.17
Week 26 (Day 182)	0.15	0.11	0.40
Week 52 (Day 364)	0.15	0.11	0.55
Log-Rank test p-values			
Celecoxib vs Diclofenac	0.533		
Celecoxib vs Ibuprofen	0.135		
Celecoxib vs NSAIDs	0.492		

Note: Event rates are based on Kaplan-Meier estimates.

Figure F1.1

Kaplan – Meier Plot of Time to Any Serious MI: Entire Study Period



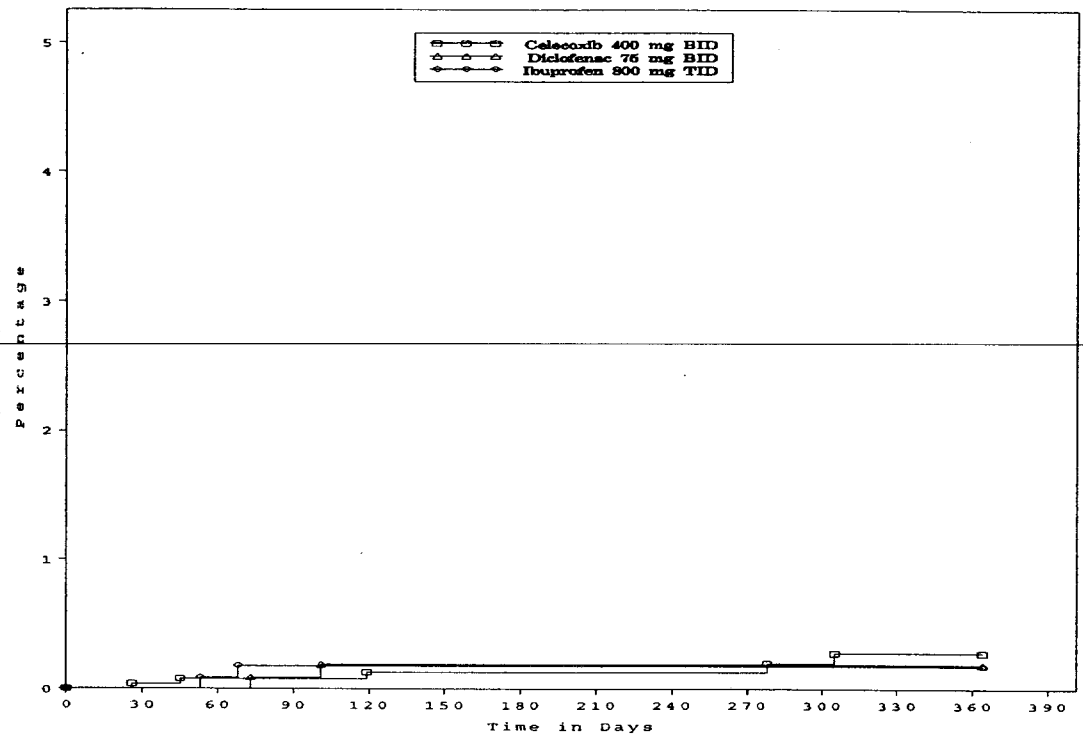
Event Rates (%)

Time Point	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
TREATED PATIENTS	3987	1996	1985
Week 1 (Day 7)	0.00	0.00	0.00
Week 4 (Day 28)	0.08	0.00	0.06
Week 13 (Day 91)	0.15	0.14	0.26
Week 26 (Day 182)	0.35	0.29	0.44
Week 39 (Day 273)	0.49	0.29	0.65
Week 52 (Day 364)	0.72	0.29	0.86
Log-Rank test p-values			
Celecoxib vs Diclofenac	0.186		
Celecoxib vs Ibuprofen	0.796		
Celecoxib vs NSAIDs	0.557		

Note: Event rates are based on Kaplan-Meier estimates.

Figure F1.2

Kaplan – Meier Plot of Time to Any Serious MI: Entire Study Period
Patients not Taking Aspirin



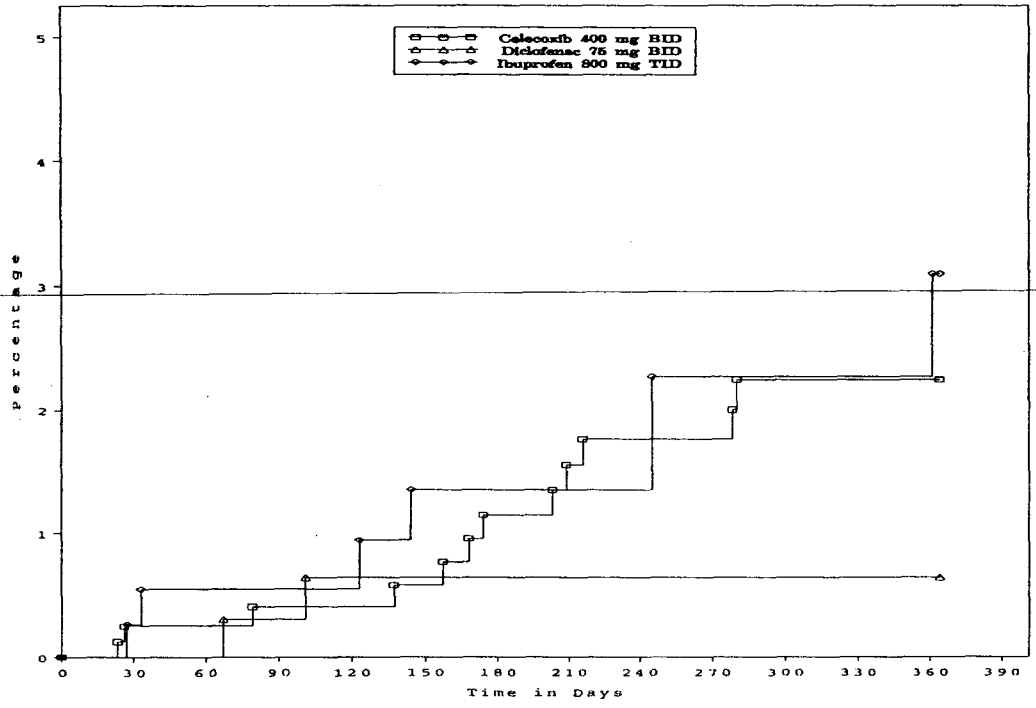
Event Rates (%)

Time Point	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
TREATED PATIENTS	3105	1551	1573
Week 1 (Day 7)	0.00	0.00	0.00
Week 4 (Day 28)	0.04	0.00	0.00
Week 13 (Day 91)	0.08	0.09	0.18
Week 26 (Day 182)	0.13	0.19	0.18
Week 52 (Day 364)	0.28	0.19	0.18
Log-Rank test p-values			
Celecoxib vs Diclofenac	0.832		
Celecoxib vs Ibuprofen	0.825		
Celecoxib vs NSAIDs	0.786		

Note: Event rates are based on Kaplan-Meier estimates.

Figure F13

Kaplan – Meier Plot of Time to Any Serious MI: Entire Study Period
Patients Taking Aspirin



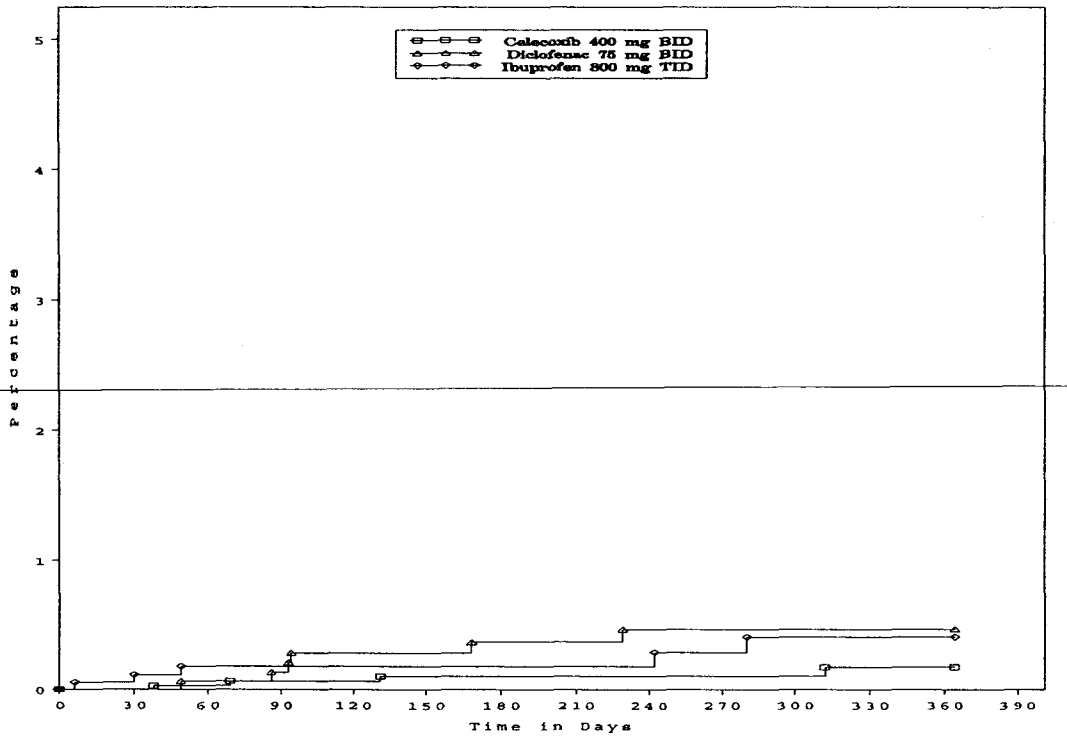
Event Rates (%)

Time Point	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
TREATED PATIENTS	882	445	412
Week 1 (Day 7)	0.00	0.00	0.00
Week 4 (Day 28)	0.25	0.00	0.27
Week 13 (Day 91)	0.41	0.30	0.55
Week 26 (Day 182)	1.15	0.64	1.35
Week 39 (Day 273)	1.76	0.64	2.27
Week 52 (Day 364)	2.24	0.64	3.10
Log-Rank test p-values			
Celecoxib vs Diclofenac	0.144		
Celecoxib vs Ibuprofen	0.678		
Celecoxib vs NSAIDs	0.593		

Note: Event rates are based on Kaplan-Meier estimates.

Figure F3.1

Kaplan – Meier Plot of Time to Any Serious Cerebrovascular Disorder: Entire Study Period



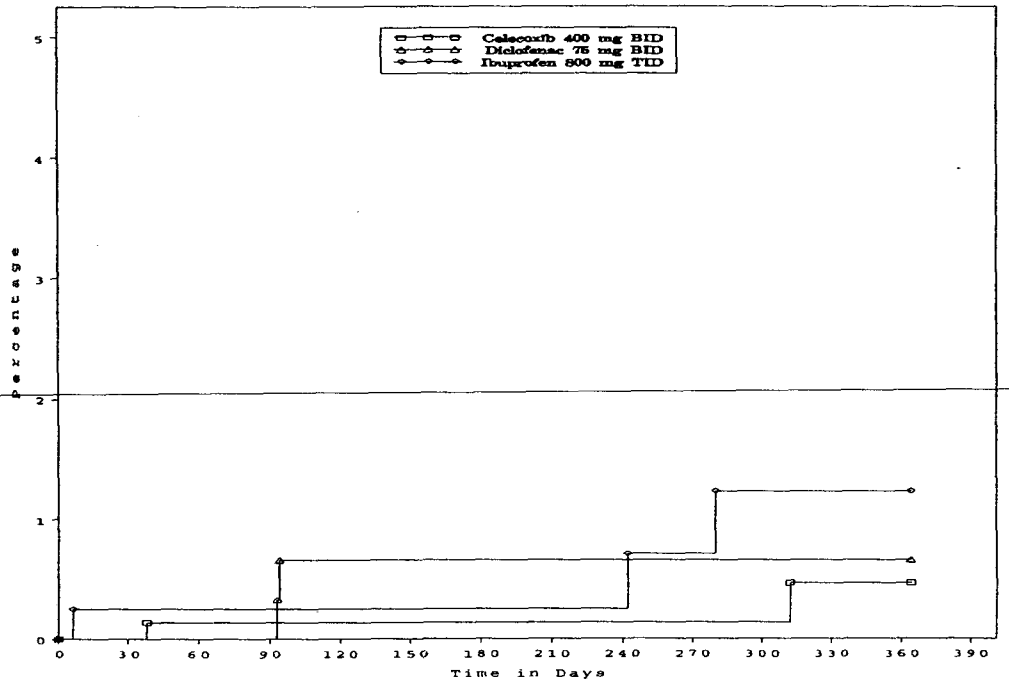
Event Rates (%)

Time Point	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
TREATED PATIENTS	3987	1996	1985
Week 1 (Day 7)	0.00	0.00	0.05
Week 13 (Day 91)	0.06	0.13	0.18
Week 26 (Day 182)	0.10	0.37	0.18
Week 39 (Day 273)	0.10	0.47	0.29
Week 52 (Day 364)	0.17	0.47	0.40
Log-Rank test p-values			
Celecoxib vs Diclofenac	0.062+		
Celecoxib vs Ibuprofen	0.138		
Celecoxib vs NSAIDs	0.057+		

Note: Event rates are based on Kaplan-Meier estimates.
***, **, *, + Statistically significant at p=0.001, 0.01, 0.05, and 0.10, respectively.

Figure F8.3

Kaplan – Meier Plot of Time to Any Serious Cerebrovascular Disorder: Entire Study Period
Patients Taking Aspirin



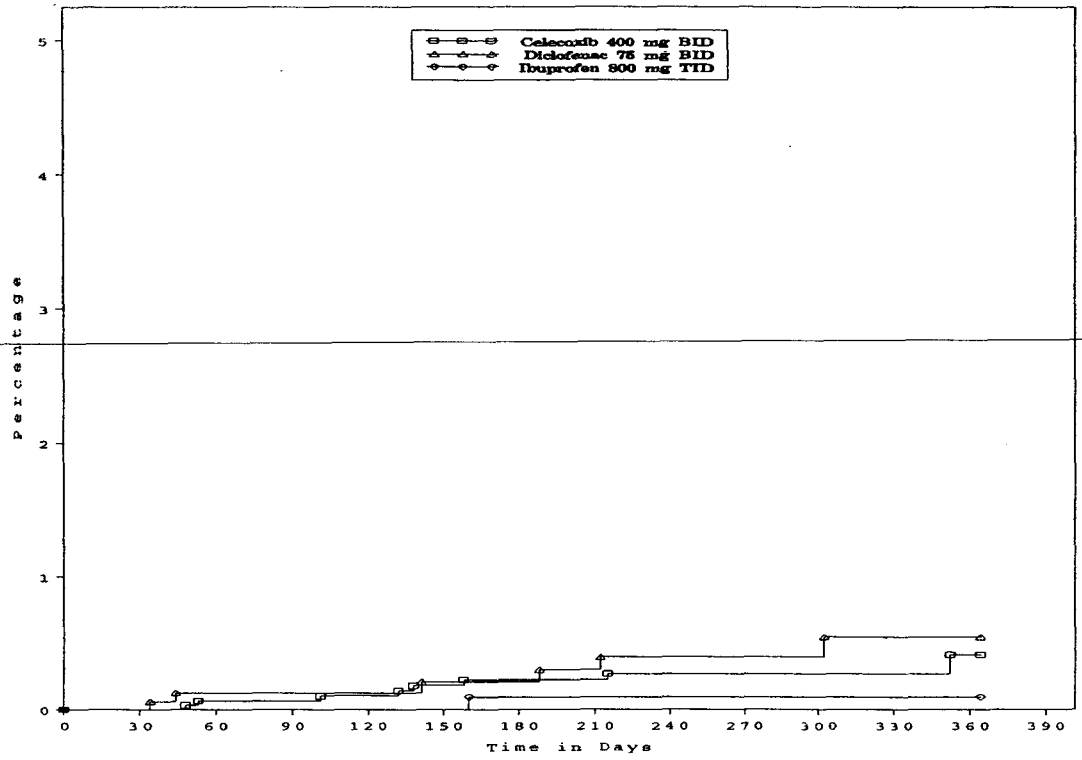
Event Rates (%)

Time Point	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
TREATED PATIENTS	882	445	412
Week 1 (Day 7)	0.00	0.00	0.25
Week 13 (Day 91)	0.14	0.00	0.25
Week 26 (Day 182)	0.14	0.66	0.25
Week 39 (Day 273)	0.14	0.66	0.71
Week 52 (Day 364)	0.46	0.66	1.23
Log-Rank test p-values			
Celecoxib vs Diclofenac	0.428		
Celecoxib vs Ibuprofen	0.191		
Celecoxib vs NSAIDs	0.224		

Note: Event rates are based on Kaplan-Meier estimates.

Figure F4.1

Kaplan – Meier Plot of Time to Any Serious DVT: Entire Study Period



Event Rates (%)

Time Point	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
TREATED PATIENTS	3987	1996	1985
Week 1 (Day 7)	0.00	0.00	0.00
Week 13 (Day 91)	0.06	0.12	0.00
Week 26 (Day 182)	0.22	0.21	0.09
Week 39 (Day 273)	0.27	0.39	0.09
Week 52 (Day 364)	0.41	0.55	0.09
Log-Rank test p-values			
Celecoxib vs Diclofenac	0.350		
Celecoxib vs Ibuprofen	0.166		
Celecoxib vs NSAIDs	0.881		

Note: Event rates are based on Kaplan-Meier estimates.

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/s/

Lawrence Goldkind
6/6/02 05:33:04 PM
MEDICAL OFFICER

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-998

Searle
Attention: Eva Essig, Ph.D.
Associate Director, Worldwide Regulatory Affairs
4901 Searle Parkway
Skokie, Illinois 60077

Dear Dr. Essig:

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Celebrex (celecoxib capsules), 100 mg/200 mg.

We have received your submission dated June 12, 2000 (to Supplement 009) reporting on the postmarketing study commitment listed in the December 31, 1998 approval letter for this application, identified as follows:

> Study the effects of Celebrex on acid-base status, including assessment of changes in serum bicarbonate, using a protocol agreed to by the review division.

We have reviewed your submission dated June 12, 2000, and conclude that the commitment listed above was fulfilled.

This completes your postmarketing commitment acknowledged in our December 31, 1998 approval letter.

Sincerely,

Jonca C. Bull, M.D.
Deputy Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Jonca Bull
7/3/01 09:50:42 AM

APPEARS THIS WAY
ON ORIGINAL

AGENCY'S REQUEST FOR PHASE 4 COMMITMENTS

(per AP letter issued on 12-31-98)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 31 1998

NDA 20-998

G.D. Searle
Attention: Winifred Begley
Director Regulatory Affairs
4901 Searle Parkway
Skokie, Illinois 60077

Dear Ms. Begley:

Please refer to your new drug application (NDA) dated June 29, 1998, received June 30, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CELEBREX (celecoxib capsules) 100mg and 200 mg.

We acknowledge receipt of your submissions dated June 29 (two); July 6, 7, 14, 16, 21 (two), 22, and 30 (three); August 4 (two), 7 (three), 10, 17, 21, 24 (two), and 27 (two); September 2 (two), 3 (two), 11, 17 (four), 18, 24 (three), 25, and 28 (two); October 1 (three), 2, 5 (two), 7, 8 (two), 13, 14 (three), 15, 16 (five), 20 (two), 21, 23 (four), 26 (three), 27 (three), 28 (four), and 30 (three); November 2, 3, 4, 5, 6 (two), 10, 11 (two), 12, 16 (two), 19 (two), 23 (two), 24, and 25; December 3, 8, 9 (two), 10 (two), 16, 18, 21, 24, and 29; and correspondence via facsimile transmission dated December 29, 1998.

The user fee goal date for this application is December 31, 1998.

This new drug application provides for the use of CELEBREX (celecoxib capsules) 100mg and 200 mg for the signs and symptoms of osteoarthritis and rheumatoid arthritis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling (package insert submitted December 29, 1998) with the revisions incorporated in the enclosed label text. Accordingly, the application is approved effective on the date of this letter.

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed label (FPL) may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20998." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated December 29, 1998. This commitment is to study the effects of Celebrex on acid-base status, including assessment of changes in serum bicarbonate, using a protocol agreed to by the review Division.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please note that any advertising and/or promotional activity of this product will be considered false and/or misleading under Section 502 of the Act if it presents suggestions or representations that COX-2 selectivity confers on the product any claims of safety beyond what has been demonstrated in clinical studies and presented in the approved labeling. Additionally, promotional activities that make or imply comparative claims about the frequency of clinically serious GI events compared to groups of NSAIDs or specific NSAIDs will be considered false and/or misleading without differences having been demonstrated in adequate, well-controlled studies. Finally, any promotional use of the endoscopic data without the qualifying explanations of that data found in the approved labeling (paragraph beginning on line 251 in the enclosed label text) will be considered false and/or misleading. If you have any questions or concerns about this matter please contact the Center for Drug Evaluation and Research's Division of Drug Marketing, Advertising and Communications.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Victoria Lutwak, Project Manager, at (301) 827-2090.

Sincerely,

/S/

Robert DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDA 20-998
HFD-550/Div. Files
HFD-550/V.Lutwak
HFD-550/Medical/Hyde/Witter/Averbuch/Villalba
HFD-550/Pharmacology/Weir/Yang
HFD-830/Chemistry/Patel/Bhavnagri
HFD-725/Statistics/Lin/Lu/Gao/Patrician/Thompson
HFD-880/Bashaw/Lee
HFD-180/Talarico/Gallo-Torres/Goldkind
HFD-110/Chen/Throckmorton
~~HF-2/MedWatch (with labeling)~~
HFD-002/ORM (with labeling)
HFD-105/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-95/DDMS (with labeling)
HFD-830/DNDC Division Director
DISTRICT OFFICE

Drafted by: vl/December 8, 1998
Initialed by:
final:
filename: 981208AP.WPD

APPROVAL (AP) (with Phase 4 Commitments)

APPEARS THIS WAY
ON ORIGINAL

SEARLE'S COMMITMENTS

SEARLE

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
FAX (847) 982-4701

December 29, 1998

Dr. Robert DeLap, M.D., Ph.D., Acting Director
Division of Anti-inflammatory, Analgesic,
and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-550)
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-998
Celebrex™ (celecoxib)

Dear Dr. DeLap,

With reference to the FDA request of December 29, 1998, regarding a phase 4 commitment, Searle commits to study the effects of Celebrex on acid-base status, including assessment of changes in serum bicarbonate, using a protocol agreed to by this Division.

The assessment for changes in serum bicarbonate are planned for studies N49-98-22-035 and N49-98-12-102 which have already been submitted to the IND (SN 364 and SN 372).

Sincerely,

Winifred M. Begley

Winifred M. Begley
Director, Regulatory Affairs

WMB/iw

PATENT STATEMENT UNDER 21 USC 355(B)(1)

Drug Substance Patent

The following U.S. Patent contains claims directed to the drug substance celecoxib, which is the subject of the present application:

Patent #	Owner	Title	Expiration
5,466,823	G.D. Searle & Co.	Substituted Pyrazolyl Benzenesulfonamides	Nov. 30, 2013

The undersigned declares that the above patent covers the drug substance celecoxib, which is the subject of this application for which approval is being sought.

Drug Product (Composition) Patent

The following U.S. Patent contains claims directed to formulations/dosage forms of the drug substance, celecoxib, which is the subject of the present application:

Patent #	Owner	Title	Expiration
5,563,165	G.D. Searle & Co.	Substituted Pyrazolyl Benzenesulfonamides for the Treatment of Inflammation	Nov. 30, 2013

The undersigned declares that the above patent covers the formulations and/or compositions of the drug substance, celecoxib. This drug product is the subject of this application for which approval is being sought.

Drug Product (Method of use) Patent

The following U.S. Patent contains claims directed to methods of using the drug substance, celecoxib, which is the subject of the present application:

Patent #	Owner	Title	Expiration
5,760,068	G.D. Searle & Co.	Substituted Pyrazolyl Benzenesulfonamides for the Treatment of Inflammation	Jun. 2, 2015

The undersigned declares that the above patent covers the methods of using the drug substance, celecoxib. This drug product is the subject of this application for which approval is being sought.

Patent Owner

The undersigned certifies that the above listed patents are assigned to G.D. Searle & Co., who is also the NDA applicant.

Eva C. Essig, Ph.D.
Associate Director, Regulatory Affairs

EXCLUSIVITY SUMMARY for NDA 20-998 SUPPL # 009

Trade Name: Celebrex™ **Generic Name: celecoxib**

Applicant Name: G.D. Searle L.L.C. **HFD-550**

Approval Date: June 07, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/___/ NO /__X__/

b) Is it an effectiveness supplement? YES /__X__/ NO /___/

If yes, what type(SE1, SE2, etc.)? **SE-8**

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /__/ NO /__X__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

This supplemental new drug application provides for

Changes to the Warnings, Precautions, Adverse Events and

Clinical Studies sections of the labeling based on a large safety outcome study for Celebrex compared to ibuprofen and diclofenac.

d) Did the applicant request exclusivity?

YES /___/ NO /__X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

---

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /__X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE

SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-998 celecoxib

NDA # 21-156 celecoxib

NDA #

2. Combination product. **n/a**

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /__X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, ~~including the published literature)~~ necessary to support approval of the application or supplement?

YES /__X__/ NO /_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /__X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # N 49-98-02-102

Investigation #2, Study # N 49-98-02-035

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /_ _/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_ **X** __/

Investigation #2 YES /___/ NO /__ **X** _/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # **N 49-98-02-102**

Investigation #_2_, Study # **N 49-98-02-035**

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND _____ YES /__X_/ NO /___/ Explain:

Investigation #2

IND _____ YES /__X__/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /__X__/

If yes, explain: _____

_____

_____

Barbara J. Gould *June 07, 2002*
Signature of Preparer Date
Title: *Project Manager*

Lawrence Goldkind, M.D. *June 07,2002*
Signature of Deputy Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lawrence Goldkind
6/7/02 09:32:50 AM

APPEARS THIS WAY
ON ORIGINAL

DEBARMENT STATEMENT

Pursuant to section 306 (k) of the Federal Food, Drug and Cosmetic Act, the applicant did not and will not employ or otherwise use in any capacity the services of any person debarred under subsection (a) or (b) in connection with this application.

Richard Shubart 2/14/01
Richard Shubart
Senior Director
Global R&D Quality Assurance

PHARMACIA

Pharmacia Corporation
Global Regulatory Affairs
4901 Searle Parkway
Skokie, Illinois 60077

17 May 2002

Lee Simon, M.D., Director
Division of Anti-inflammatory, Analgesic
and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-550)
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 20-988 (S-009)
Celebrex® (celecoxib)

Dear Dr. Simon:

Please refer to our meeting of May 14, 2002 regarding determination of a uniform cutoff point for Kaplan-Meier (K-M) cumulative rates in CLASS for GI and adverse events data presented in the Clinical Studies, Warnings, Precautions and Adverse Reactions sections of the Celebrex label.

We have reviewed weekly K-M estimates of the rates and numbers of patients remaining at risk (Tables T1-T10, T21.2b-c, T300.1, T300.2, T301.1, T301.2, T302.1 thru T305.1). We have selected the common cutoff point to be Week 39 (that is, 9 months) for all K-M rates quoted in the Celebrex label. This time point balances the effort to maximize the usable information from the study and minimize the variability in rates due to tail-instability, under the constraint of choosing a common cutoff point.

We have selected the common point of week 39 (9 months) for the following reasons:

- The 9 month cutoff point represents the median duration of treatment for both the Celebrex and diclofenac groups.
- At this time point, the numbers of patients remaining at risk for most of the analyses used in the label exceeded 500.

After this time point, the data demonstrates a considerable amount of variability and tail instability in certain subgroups. An example of this instability can be seen in Table T6 between Week 39 and Week 40 for celecoxib. In fact in Table 5 of the label, the numbers of patients remaining at risk in the smaller subsets are as follows:

All Patients/Celebrex with ASA:	472
Patients < 65yr/Celebrex with ASA:	248
Patients ≥ 65yr/Celebrex with ASA:	224

PHARMACIA

Pharmacia Corporation
Global Regulatory Affairs
4901 Searle Parkway
Skokie, Illinois 60077

May 9, 2002

Lee Simon, M.D., Director
Division of Anti-inflammatory, Analgesic
and Ophthalmologic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 20-998/S-009
Celebrex® (celecoxib)

Dear Dr. Simon:

Please find attached the latest version of the CLASS label dated May 9, 2002.

As per Dr. Goldkind's recommendations discussed on May 3, we have made the following changes:

- Hematological Events: We have deleted the table as requested and included the all patient event data in the text. Relative risk ratios and non-ASA and ASA cohort data have been eliminated as requested. In their place, and pursuant to Dr. Goldkind's suggestion, we have introduced a qualitative statement regarding the lower incidences of hemoglobin reductions in the celecoxib group in these two subgroups.

- Withdrawal/SAEs: We have removed the two tables with the individual event data for withdrawals and serious CV events as requested. Since ASA was a confounding variable, we have also included the non-ASA rates for the serious CV thromboembolic events. As the CV thromboembolic group is primarily composed of MI we have included the all patient and non-ASA patient rates for the Celebrex group. We believe that this is in concert with Dr. Goldkind's request that no cross-treatment comparisons are made for the individual SAEs.

With regards to other sections of the label, we provide the following:

- "Use with ASA": A minor modification has been made to describe the result for the primary endpoint.
- "Warnings": Addition of group numbers (n) has been made to Table 5. We have provided the ASA/non-ASA cohorts data for "Patients without History of Ulcer" and for "Patients with History of Ulcer". Since the cohort sizes are very small at 12 months, we have provided all rates at 48 weeks as a more robust endpoint.

PHARMACIA

Pharmacia Corporation
Global Regulatory Affairs
4901 Searle Parkway
Skokie, Illinois 60077

May 1, 2002

Lee Simon, M.D., Director
Division of Anti-inflammatory, Analgesic
And Ophthalmologic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 20-998 (S-009)
Celebrex® (celecoxib)

Dear Dr. Simon:

We would like to acknowledge FDA's revised version of the CLASS label dated April 26 and have enclosed a counter proposal for your consideration. As advised by telephone, the main areas where we are unable to reach consensus on the presentation of the data in the label related to the Adverse Reactions section, namely Table 7 (Hemoglobin Reductions), Table 8 (Withdrawals due to AEs) and Table 9 (Serious CV AEs). In order to facilitate your understanding of our revised proposal we would like to make the following comments:

General

- In making our decisions on the presentation of the data throughout the label, we have followed the recommendations of the Dispute Resolution prepared by Dr. Woodcock (see attached).
- In our review of the latest FDA proposal, we note deviations from this ruling.

Withdrawal and Serious CV AEs Tables

- [redacted] tated:

  [redacted]

  Please note that the table referred to is Table 2 in our proposed version of the label dated April 30, 2001, submitted with the Dispute Resolution.

  In your textual summary of the data, you have provided the K-M cumulative rates for investigator-reported serious CV thromboembolic events in all patients. This approach deviates from the above ruling of the Dispute Resolution and from the discussion at the Dispute Resolution meeting in the following ways:

  1. These important individual event data are not presented as a data table as stated in the ruling. In fact, the text only includes a composite of serious CV AEs and not the agreed upon individual AE data.

PHARMACIA

Pharmacia Corporation
Global Regulatory Affairs
4901 Searle Parkway
Skokie, Illinois 60077

April 23, 2002

Lee Simon, M.D., Director
Division of Anti-inflammatory, Analgesic
and Ophthalmologic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 20-998 (S-009)
Celebrex™ (celecoxib)

Dear Dr. Simon:

With reference to your fax requests of April 19 and April 22 enclosed are the following:

1. As requested by FDA, Tables 18.1-3 show the incidences of serious CV events for patients with a history of MI NOS-ICD9 code 410.9/angina pectoris NEC/NOS-ICD9 code 413.9 (all, patients not on aspirin, patients on aspirin, respectively). No differences among groups were observed but the analysis was based on small numbers of patients in the defined groups. The corresponding crude incidence rates are shown in Tables 19.1-3.

2. In addition to your request we are also providing a more robust analysis, patients for whom aspirin prophylaxis was indicated were analyzed (patients with a history of MI, CAD or coronary procedure, angina, TIA or CVA--see complete list of ICD9 codes in Table 22). These K-M curves and summary statistics are shown in Tables 20.1-3. As above no differences in rates were observed. The corresponding crude incidence rates are shown in Tables 21.1-3.

3. K-M plots of overall SAEs (Table 16), withdrawals for adverse events (Table 17), edema or hypertension (Tables 23-25), these KM support the data currently in the draft label.

Sincerely,

Winfred M. Begley

for Eva Essig, PhD
Director, Global Regulatory Affairs
(847) 982-8980
(847) 982-7883 (fax)

Enclosures

EE/nb

PHARMACIA

Pharmacia Corporation
Global Regulatory Affairs
4901 Searle Parkway
Skokie, Illinois 60077

April 17, 2002

Lee Simon, M.D., Director
Division of Anti-inflammatory, Analgesic
and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-550)
9201 Corporate Boulevard
Rockville, MD 20850

NDA 20-998 S-009
Celebrex® (celecoxib)

Dear Dr. Simon:

Please refer to our April 8 submission with a revised label for Celebrex.

As per Dr. Koestler's discussion with Dr. Bull and the Division on April 17, we now provide a revised label with certain minor edits. The sections that have been further edited are as follows:

- Use with Aspirin: A minor modification to the patient inclusion description (lines 266-271) was made to state that patients with CV disease were not excluded from the study.

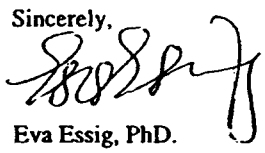
- Precautions: A change in the "Hematological Events" (lines 454-458) section was made to more clearly describe the comparisons between the Celebrex and placebo groups.

- Adverse Reactions: We removed the term "selected" from the title of Table 9 and included the descriptor "fatal and non-fatal" to define "MI" in the table. We continue to maintain that both Tables 8 and 9 provide very useful information to the prescriber. This is consistent with the ruling on the Dispute Resolution Request in which Dr. Woodcock states that the withdrawal rates and serious adverse events add value to the current label and that a data table should remain in the label.

The above changes add to our previous proposal for inclusion of relative risk and/or confidence internals to describe the important hemoglobin data derived from this study.

As we have stated, we are committed to reaching resolution of our labeling supplement. We understand from our discussions today that we should anticipate a proposed label from the Division on Friday afternoon. We will then have a teleconference on April 23 to further discuss the label and reach resolution.

Sincerely,



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April 8, 2002

Lee Simon, M.D., Director
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Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 20-998/S-009
Celebrex® (celecoxib)

Dear Dr. Simon:

Please refer to our teleconference of March 18, 2002 and a discussion with Dr. Bull on April 5. We now provide revised Celebrex labeling. Our proposal includes the following:

1. Use with Aspirin: We have made some grammatical adjustments to the sentence regarding the primary endpoint to more accurately describe the results without any material effect on the content.

2. Precautions/Geriatric Use: Pursuant to your suggestion at our March 8, 2001 meeting, we have qualified "NSAIDs" as "specific and non-specific COX-2 inhibitors".

3. Adverse Reactions/Hematological Events: In recognition of Dr. Bull's voicemail message of April 2 and as conveyed to her by phone on April 5, we have agreed to remove from the description of the hemoglobin data all mention of p-values and terms to describe statistical significance, such as "significantly". In their place, we propose use of relative risk as a means to connote important safety information. Inclusion of relative risk is entirely consistent with many examples of other FDA approved labeling as it provides meaningful information for the prescriber. We would be equally amenable to including confidence intervals in conjunction with relative risk- please refer to the alternate option. We have retained all the FDA suggested wording in text. Furthermore, also discussed at our last meeting, we have placed all the data in a table including the non-ASA and ASA results.

The proposed text reads as follows:

Hematological Events:
In this study, the incidence of clinically significant decreases in hemoglobin (>2 g/dL) confirmed by repeat testing was lower in patients on CELEBREX 400 mg BID (see Special Studies-*Use with Aspirin*) compared to patients on either diclofenac 75 mg

APPEARS THIS WAY
ON ORIGINAL