

NDA SUPPL AMENDMENT

SEARLE
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PHONE (847) 982-7000
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October 20, 2000

Jonca Bull, M.D.
Director
Division of Anti-inflammatory, Analgesic
and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-5)
9201 Corporate Boulevard
Rockville, MD 20850



BM
SE8-009

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

Dear Dr. Bull,

With reference to a fax received ^{October 5} ~~November 5~~, 2000 regarding our supplement S-009 we enclose our response to the question posed.

Please contact the undersigned if you require any further clarification.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

cc: Y. Kong Pharm. D.

ORIGINAL

DUPLICATE

SEARLE

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077
PHONE (847) 982-7000
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November 3, 2000

Jonca Bull, 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

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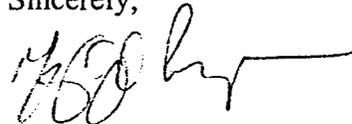
Re: NDA 20-998 S/009
Celebrex® (celecoxib)

Dear Dr. Bull,

With reference to a fax received October 25, 2000 regarding our supplement S-009 we enclose our response to the question posed.

Please contact the undersigned if you require any further clarification.

Sincerely,


for Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

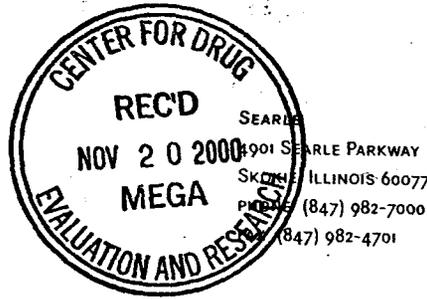
cc: Y. Kong Pharm. D.

Enc.
WB/jr

SEARLE

November 17, 2000

Jonca Bull 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



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

Dear Dr. Bull,

Enclosed are the following:

- A revised side-by-side presentation of the draft label for Celebrex showing changes and cross-references to supporting data
- A revised marked-up version of the Final Printed Label including the proposed changes

The revisions made are listed on the attached document. The reason for the revisions is that these documents were found to have inconsistencies when compared to the WORD version of the label that was submitted both in paper and electronic form on June 12, 2000.

If you have any questions regarding this submission, please contact the undersigned.

Sincerely,

Winifred M. Begley
 Senior Director
 Regulatory Affairs
 (847) 982-8155
 (847)-982-8090

cc Y. Kong Pharm.D. (15 desk copies)

ORIGINAL

SEARLE



November 21, 2000

Jonca Bull, 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

Bm
SE8-009

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

Dear Dr. Bull:

Further to the facsimile of 11/16/00, we submit the following tables and supporting documentation. If we have misunderstood any of your requests, please let us know and we shall remediate the situation promptly.

I. Additional Analyses for Laboratory Data

A. Below please find the reviewer's table with blank boxes filled in as requested. These data are derived from Table T45.1 in the submission and attached Tables T5.1 – T6.2. Patients with an extreme value at baseline were excluded from these analyses. Patients with an extreme value at baseline and their laboratory data for the remaining time they were in the study are listed in attached Appendices 1–6.2.

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Extreme Laboratory Values from Entire Study Period ^a

Lab Test	Celecoxib 400 mg BID N (%)	Diclofenac 75 mg BID N (%)	Ibuprofen 800 mg TID N (%)
BUN (mmol/l)			
>6.7 ^d	1281/3141 (40.8)	549/1552 (35.4) *	513/1539 (33.3) *
>14.3 ^d	31/3692 (0.8)	20/1849 (1.1)	16/1786 (0.9)
Creatinine (mmol/l)			
>133 ^c	41/3684 (1.1)	37/1848 (2.0) *	30/1786 (1.7) *
>265.2 ^c	1/3692 (<0.1)	0/1850 (0)	0/1786 (0)
Potassium (meq/l)			
<3.5	89/3670 (2.4)	46/1836 (2.5)	116/1766 (6.6) *
<3.0	7/3673 (0.2)	7/1837 (0.4)	11/1770 (0.6) *
>5.0	406/3657 (11.1)	182/1825 (10.0)	119/1758 (6.8) *
>6.0	11/3673 (0.3)	3/1837(0.2)	0/1170 (0)
Chloride (mmol/l)			
<75	0/3690 (0)	0/1847 (0)	0/1786 (0)
<90	7/3690 (0.2)	1/1847 (<0.1)	4/1786 (0.2)
>110	86/3690 (2.3)	28/1847 (1.5) *	51/1785 (2.9)
>120	0/3690 (0)	0/1847 (0)	0/1786 (0)
Bicarbonate (mmol/l)			
<20	44/3687 (1.2)	22/1844 (1.2)	34/1782 (1.9) *
<15	1/3689 (<0.1)	2/1844 (0.1)	0/1782 (0)
>35	13/3689 (0.4)	7/1844 (0.4)	3/1782 (0.2)
Phosphate (mmol/l)			
<0.32	0/3676 (0)	0/1841 (0)	0/1771 (0)
<0.64	19/3676 (0.5)	16/1841 (0.9)	15/1771 (0.8)
<0.96	791/3572 (22.1)	471/1775 (26.5) *	399/1709 (23.3)
>2.10	0/3676 (0)	1/1841 (<0.1)	1/1771 (<0.1)
>2.42	0/3676 (0)	0/1841 (0)	1/1771 (<0.1)

- a. Data from electronic submission table T45.1 and at request of reviewer.
- b. Differs from celecoxib at p <= 0.05
- c. Correspond to a serum creatinine of 1.5 and 3.0 mg/dl, respectively.
- d. Corresponds to a BUN of 20 and 40 mg/dl, respectively.

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ON ORIGINAL**

- B. Below please find the requested BUN and Creatinine contingency table. Analyses of these data segregated by aspirin use were not performed as part of the submission and have therefore been provided in this response. These data are derived from Table T48 in the submission and attached Tables T4.1.1 – T4.2.3.

Incidence of Combined Abnormalities in BUN and SCr ^{a,b}

Parameter	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
	N (%)	N (%)	N (%)
BUN ≥ 14.3 mmol/l and SCr ≥ 159 mmol/l ^c	14/3702 (0.4)	6/1852 (0.3)	7/1807 (0.4)
BUN ≥ 6.7 and SCr ≥ 133 mmol/l ^d	50/3702 (1.4)	43/1852 (2.3)	32/1807 (1.8)

a. Data from electronic datasets Table T48 and at request of reviewer from sponsor.

b. SCr = serum creatinine

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

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

Incidence of Combined Abnormalities in BUN and SCr Grouped by ASA Use ^{a,b}

Parameter	Celecoxib 400 mg BID		Diclofenac 75 mg BID		Ibuprofen 800 mg TID	
	N (%)		N (%)		N (%)	
	ASA	No ASA	ASA	No ASA	ASA	No ASA
BUN ≥ 14.3 mmol/l and SCr ≥ 159 mmol/l ^c	5/834 (0.6)	9/2868 (0.3)	1/423 (0.2)	5/1429 (0.4)	3/390 (0.8)	4/1417 (0.3)
BUN ≥ 6.7 and SCr ≥ 133 mmol/l ^d	12/834 (1.4)	38/2868 (1.3)	17/423 (4)	26/1429 (1.8)	11/390 (2.8)	21/1417 (1.5)

a. Data from electronic datasets Table T48 and at request of reviewer from sponsor.

b. SCr = serum creatinine

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

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

APPEARS THIS WAY
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C. We are unable to provide data on extreme high criterion for maximum BP recorded at any time during the trial as BP measurements were obtained as part of the physical examination, which was required only at baseline and the final visit.

Analyses of extreme high criterion for maximum BP at the final visit segregated by aspirin use were not performed as part of the submission and have therefore been provided in this response. These data are derived from Table T45 in the submission and attached Tables T8.1-T8.2.

Incidence of BP Elevations During Study ^a

Parameter	Celecoxib 400 mg BID N (%)	Diclofenac 75 mg BID N (%)	Ibuprofen 800 mg TID N (%)
Sitting Systolic BP ≥ 15% increase over baseline			
All Patients	315/2925 (10.8)	163/1434 (11.4)	173/1387 (12.5)
Patients taking ASA	82/653 (12.6)	38/327 (11.6)	39/287 (13.6)
Patients not taking ASA	233/2272 (10.3)	125/1107 (11.3)	134/1100 (12.2)
Sitting Diastolic BP ≥ 15% increase over baseline			
All Patients	298/2925 (10.2)	146/1434 (10.2)	134/1387 (9.7)
Patients taking ASA	70/653 (10.7)	33/327 (10.1)	30/287 (10.5)
Patients not taking ASA	228/2272 (10.0)	113/1107 (10.2)	104/1100 (9.5)

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

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II. Additional Analyses for SAEs

A./B. Table of Serious Adverse Events/ Reported Serious Renal and Cardiac Adverse Events

B. Below please find the table of selected serious adverse events relevant to renal and cardiac safety with the missing incidence calculated. These data are derived from Table T43 in the submission and attached Tables T1.1-T1.4.

Serious Adverse Events (SAEs) Reported During the Study ^a

Lab Test	Celecoxib 400 mg BID N (%)	Diclofenac 75 mg BID N (%)	Ibuprofen 800 mg TID N (%)
Renal SAEs			
Hyper-, Hypo-kalemia ^c	0 (0)	0 (0)	0 (0)
Acidosis ^c	0 (0)	0 (0)	0 (0)
Nephrotic Syndrome ^c	0 (0)	0 (0)	0 (0)
Edema ^c	0 (0)	0 (0)	0 (0)
Uremia	0 (0)	0 (0)	1 (<0.1)
Renal Calculus	4 (0.2)	0 (0)	2 (0.2)
Cardiac SAEs			
Atrial Arrhythmias			
Arrythmia Atrial	2 (<0.1)	0 (0)	1 (<0.1)
Bradycardia	2 (<0.1)	0 (0)	0 (0)
Fibrillation Atrial	9 (0.4)	2 (0.2)	3 (0.3)
Tachycardia	3 (0.1)	0 (0)	0 (0)
Supraventricular Combined Atrial SAEs ^b	14 (0.6)	2 (0.2)	4 (0.4)
Angina			
Unstable angina	8 (0.3)	4 (0.4)	0 (0)
Angina Pectoris	4 (0.2)	5 (0.5)	6 (0.5)
Coronary Artery Disorder	19 (0.8)	5 (0.5)	5 (0.4)
Combined Anginal Disorders ^c	30 (1.3)	14 (1.3)	10 (0.9)
Myocardial Infarction	19 (0.8)	4 (0.4)	9 (0.8)
Hypertension Aggravated	2 (<0.1)	0 (0)	0 (0)
Thrombophlebitis Combined ^d	8 (0.34)	6 (0.56)	1 (0.09)

- a. Data from electronic submission table T43. Incidence reported per 100 person-years.
- b. Sum of atrial arrhythmia, atrial fibrillation, bradycardia and tachycardia. If a patient had more than one SAE within a body system, that patient is counted once in the overall incidence.
- c. Includes unstable angina, angina pectoris and coronary artery disorder.
- d. Includes Aes reported under the following terms: phlebitis, thrombophlebitis, thrombophlebitis arm, thrombophlebitis deep, thrombophlebitis leg, thrombophlebitis leg deep, thrombophlebitis leg superficial.
- e. These SAEs were not reported by Investigators.

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III. Changes in Laboratory Parameters

A. Extreme Changes from Baseline

B. The results of extreme analyses using different cut-points are shown in the table on page 1. Results of analyses using the same cut-points but segregating by aspirin use are shown in the table on the following page. These data are derived from Appendices 2.11.2.1 and 2.11.2.2. of the submission and attached Tables T6.1-T7.6.3.

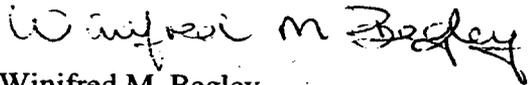
Extreme Laboratory Values from Entire Study Period by ASA Use ^a

Lab Test	Celecoxib 400 mg BID N (%)		Diclofenac 75 mg BID N (%)		Ibuprofen 800 mg TID N (%)	
	ASA	No ASA	ASA	No ASA	ASA	No ASA
BUN (mmol/l)						
>6.7 ^d	280/658 (42.6)	1001/2483 (40.3)	117/322 (36.3)	432/1230 (35.1) *	115/312 (36.9)	398/1227 (32.4) *
>14.3 ^d	12/829 (1.4)	19/2863 (0.7)	9/421 (2.1)	11/1428 (0.8)	5/386 (1.3)	11/1400 (0.8)
Creatinine (mmol/l)						
>133 ^c	9/826 (1.1)	32/2858 (1.1)	14/421 (3.3) *	23/1427 (1.6)	10/386 (2.6)	20/1400 (1.4)
>265.2	1/829 (0.1)	0/2863 (0)	0/422 (0)	0/1428 (0)	0/386 (0)	0/1400 (0)
Potassium (meq/l)						
<3.5	10/824 (1.2)	79/2846 (2.8)	9/419 (2.1)	37/1417 (2.6)	20/383 (5.2) *	96/1383 (6.9) *
<3.0	0/824 (0)	7/2849 (0.2)	1/420 (0.2)	6/1417 (0.4)	3/383 (0.8) *	8/1387 (0.6)
>5.0	95/820 (11.6)	311/2837 (11.0)	56/416 (13.5)	126/1409 (8.9) *	40/383 (10.4)	79/1375 (5.7) *
>6.0	0/824 (0)	11/2849 (0.4)	1/420 (0.2)	2/1417 (0.1)	0/383 (0)	0/1387 (0)
Chloride (mmol/l)						
<75	0/829 (0)	0/2861 (0)	0/422 (0)	0/1425 (0)	0/386 (0)	0/1400 (0)
<90	0/829 (0)	7/2861 (0.2)	0/422 (0)	1/1425 (<0.1)	1/386 (0.3)	3/1400 (0.2)
>110	25/829 (3.0)	61/2861 (2.1)	6/422 (1.4)	22/1425 (1.5)	14/385 (3.6)	37/1400 (2.6)
>120	0/829 (0)	0/2861 (0)	0/422 (0)	0/1425 (0)	0/386 (0)	0/1400 (0)
Bicarbonate (mmol/l)						
<20	8/829 (1.0)	36/2858 (1.3)	4/421 (1.0)	18/1423 (1.3)	10/385 (2.6) *	24/1397 (1.7)
<15	0/829 (0)	1/2860 (<0.1)	1/421 (0.2)	1/1423 (<0.1)	0/385 (0)	0/1397 (0)
>35	5/829 (0.6)	8/2860 (0.3)	1/421 (0.2)	6/1423 (0.4)	0/385 (0)	3/1397 (0.2)
Phosphate (mmol/l)						
<0.32	0/824 (0)	0/2852 (0)	0/421 (0)	0/1420 (0)	0/383 (0)	0/1388 (0)
<0.64	3/824 (0.4)	16/2852 (0.6)	4/421 (1.0)	12/1420 (0.8)	2/383 (0.5)	13/1388 (0.9)
<0.96	171/796 (21.5)	620/2776 (22.3)	102/407 (25.1)	369/1368 (27.0) *	80/367 (21.8)	319/1342 (23.8)
>2.10	0/824 (0)	0/2852 (0)	0/421 (0)	1/1420 (<0.1)	0/383 (0)	1/1388 (<0.1)
>2.42	0/824 (0)	0/2852 (0)	0/421 (0)	0/1420 (0)	0/383 (0)	1/1388 (<0.1)

- a. Data from electronic submission appendix 2.11.2.1 and 2.11.2.2 and at request of reviewer. Shown are maximum values from any time relative to baseline
- b. Corresponds to a serum creatinine of 1.5 and 3.0 mg/dl, respectively.
- c. Corresponds to a BUN of 20 and 40 mg/dl, respectively.
- * p <= 0.05 versus celecoxib

Please contact the undersigned if you require any further clarification.

Sincerely,



Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

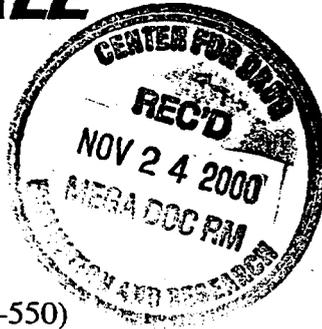
Enclosures

WMB/sks

cc: Y. Kong Pharm. D.
D. Throckmorton, M.D.

**APPEARS THIS WAY
ON ORIGINAL**

SEARLE



SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

November 22, 2000

Jonca Bull, 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 20-998 S-009
Celebrex® (celecoxib)

NDA 20-998 S-009

Dear Dr. Bull:

Further to the facsimile of 11/17/00, we submit the following:

Bm
SEP-009

1. Confirm the accuracy of the attached table.
2. Create a similar table for mortality and cardiovascular mortality based on the use of ASA by the patients.

Please see the table below. There were 36 deaths during the study; 16 occurred during treatment or within 28 days after discontinuation of treatment, 20 occurred more than 28 days after discontinuation of treatment.

Incidence of Death (No. per 100 pt.-yr) ^a

	Celecoxib 400 mg BID (n = 3987)	Diclofenac 75 mg BID (n = 1996)	Ibuprofen 800 mg TID (n = 1985)
Deaths - all causes	19 (0.8)	9 (0.8)	8 (0.7)
Deaths - cardiac ^b	11 (0.5)	5 (0.5)	5 (0.4)

- a. Data from Appendix 2.9.1 (vol 24 of 98 pages 3918-3920); includes all deaths reported during the study.
- b. Includes deaths due to ischemic cardiac causes (MI, cardiac arrest, CAD, cerebrovascular disorder, atherosclerotic cardiovascular disease; excludes 2 cases of CHF)

Incidence of Death Stratified by Aspirin Use (No. per 100 pt.-yr) ^a

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Deaths - all causes			
Aspirin users	6 (1.2)	1 (0.4)	4 (1.6)
Non-aspirin users	13 (0.7)	8 (1.0)	4 (0.5)
Deaths - cardiac ^b			
Aspirin users	5 (1.0)	0 (0)	3 (1.2)
Non-aspirin users	6 (0.3)	5 (0.6)	2 (0.2)

- a. Data from Table T9 (attached); includes all deaths reported during the study.
- b. Includes deaths due to ischemic cardiac causes (MI, cardiac arrest, CAD, cerebrovascular disorder, atherosclerotic cardiovascular disease; excludes 2 cases of CHF)

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Celebrex® (celecoxib)

NDA 20,998 S-009

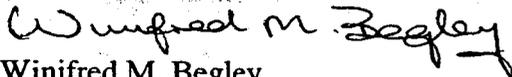
Page 2

1. Consider whether a time-to-event analysis for the deaths similar to what was done with the original celecoxib NDA, would be of interest.

Kaplan-Meier plots of time to death for all patients, those taking aspirin and those not taken aspirin are attached (Tables T10.1- T10.3). Rates are not statistically significantly different between treatment groups for any cohort analyzed. It should be noted that the denominator after 360 days is so small that the effect of individual deaths is exaggerated and that such differences are not clinically meaningful. Rates are marginally higher in patients taking aspirin presumably because of the underlying increased mortality rates associated with cardiovascular disease.

Please contact the undersigned if you require any further clarification.

Sincerely,



Winifred M. Begley

Senior Director

Regulatory Affairs

(47) 982-8155

(847)-982-8090

Enclosures

WMB/sks

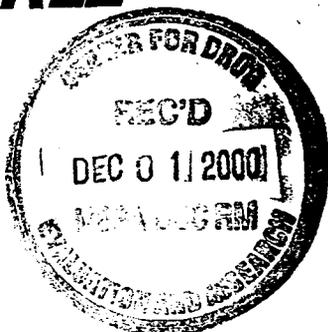
cc: Y. Kong Pharm. D.
D. Throckmorton, M.D.

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SEARLE

NEW CORRESP

NE



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November 30, 2000

Dr. Michael Bull, 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)
101 Corporate Boulevard
Rockville, MD 20850

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

Dear Dr. Bull,

Below are our responses to questions from Dr. Throckmorton's and Dr. Witter received by phone.

Dr. Throckmorton

Appendix 2.9.1 Listing of deaths
The RxDay column corresponds to the day of death, days on trt indicates the number of days of double-blind
treatment. From these columns one can calculate the number of days after the last dose when the death
occurred. Please let me know if you want a list of the subtractions from the columns?

Dr. Witter

Section 10.3 of study N49-00-06-035-102 contains the section on Deaths and other Serious Adverse Events.
The Appendix 2.9.1 lists the patients who died and Appendix 2.15 includes narratives of the deaths.

Appendix 2.14 Summary of concurrent Medication, pages 25-27 under the category CYCLO-OXYGENASE
include all of the NSAIDs. In this table one cannot distinguish between OTC or Rx, however, if there are specific
requests regarding specific drugs we can produce specific listings of the CRF text, dosing, as well as duration.
Please advise if you want specific OTC NSAIDs.

Kind regards,

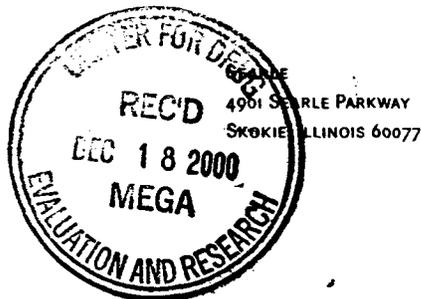
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cc: Y. Kong Pharm. D.

SEARLE



December 14, 2000



Jonca Bull, 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 20-998 S/009
Celebrex® (celecoxib)

Dear Dr. Bull,

Below is our response to your fax dated 11/29/2000 requesting information regarding Study N 499-99-02-123.

If you have any questions concerning this submission please contact the undersigned.

Kind regards,

Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

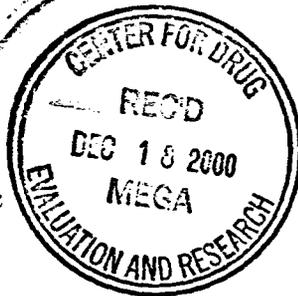
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SEARLE



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4901 SEARLE PARKWAY
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December 14, 2000

Jonca Bull, 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 20-998 S/009
Celebrex® (celecoxib)

Dear Dr. Bull,

Enclosed is our response to your fax dated 12/13/00 requesting a dataset for ITT patients.

If you have any questions or need additional information, please do not hesitate to contact me.

Kind regards,

A handwritten signature in cursive script that reads 'Winifred M. Begley'.

Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

cc: Y. Kong Pharm. D.

WB/jr

ORIGINAL

SEARLE



December 15, 2000

Jonca Bull, 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 20-998 S/009

Celebrex® (celecoxib)

Dear Dr. Bull,

Below are our responses to questions from Dr. Throckmorton's regarding performing additional analyses received by fax dated 12/6/00.

Also enclosed is an additional analysis that was created to examine if NSAIDs and COX-2 inhibitors might have differential effects on patients with normal creatinine at baseline segregated into two groups based on BUN.

Kind regards,

Winifred M. Begley

Winifred M. Begley
 Senior Director
 Regulatory Affairs
 (847) 982-8155
 (847)-982-8090

NH
12/24/00
W.T. W

cc: Y. Kong Pharm. D.

WB/jr

ORIGINAL

SEARLE

December 15, 2000

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

NDA SUPPL AMENDMENT

Jonca Bull, 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

Bm
SE8-009



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

Dear Dr. Bull,

Enclosed is our response to your fax dated 12/6/00 requesting clinical information related to Appendix 2.15 and 2.14.

If you need additional information concerning this submission please do not hesitate to contact me.

Sincerely,

A handwritten signature in cursive that reads "Winifred M. Begley".

Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

cc: Y. Kong Pharm. D.

WB/jr

SE8-009 c

SEARLE

December 21, 2000

Kathleen Reedy HFD 21
Food and Drug Administration
5630 Fishers Lane Room 1093
Rockville, MD 20897



SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

Re: **NDA 20-998 S/009**
Arthritis Advisory Committee on
Celebrex® (celecoxib)
February 7, 2001

Dear Kathleen,

With reference to the up-coming FDA Advisory Committee meeting on February 7, 2001 I am pleased to provide, as you requested, 40 bound copies of a fully releasable Briefing Document. An additional unbound copy is provided along with an electronic pdf file (disk attached) for the website.

Please note that the hard copy and pdf have the following blank pages, as these mark the end of a section. The pages are: 4, 15, 59, 67, 91, 95.

Please contact me if anything further is needed.

Kind regards,

Winifred M. Begley
Senior Director
Regulatory Affairs
Tel (847)-982-8155
Fax (847)-982-8090

CC: Y. Kong Pharm D.
Enclosures

WB/jr

ORIGINAL

SEARLE

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

January 5, 2001

Jonca Bull, 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 20-998 S/009
Celebrex® (celecoxib)

Dear Dr. Bull,

Enclosed is our response to your fax dated 1/3/01 with respect to ASA and non-ASA users.

If you need additional information concerning this submission please do not hesitate to contact me.

Sincerely,

Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

cc: Y. Kong Pharm. D.
D. Throckmorton, M.D.

WB/jr

FDAClass01052001.doc

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SEARLE

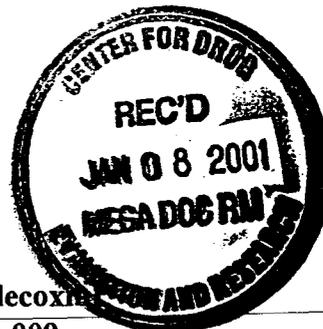
SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

January 5, 2001

Jonca Bull, 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

NON-CLERICAL MOVEMENT

*BB
588-009*



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

Dear Dr. Bull,

had desk

Enclosed is our response to the PK question in your fax dated 1/3/01.

If you have any questions regarding this submission please contact the undersigned

Sincerely,

Winifred M. Begley

Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

cc: Y. Kong Pharm. D.

WB/jr

ORIGINAL

OTC use
+ related
NSAID
category

SEARLE

NDA ORIG AMENDMENT
NR

January 5, 2001

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

Jonca Bull, 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



Celebrex® (celecoxib)
NDA 20,998 S-009
Meeting Request Type B

Dear Dr. Bull,

We would like an opportunity to discuss the CLASS study results with the agency before the Advisory Committee meeting on February 7th. We propose the following questions as potential points of discussion:

1. Does the CLASS study support the conclusion that celecoxib is associated with a decreased incidence of symptomatic ulcers and/or ulcer complications versus comparator NSAIDs?
2. If so, what are the conditions under which this conclusion is supportable taking into account duration of treatment, individual comparator NSAIDs, and patient risk factors (including concomitant use of low dose aspirin)?
3. Are the data on decreases in hematocrit and hemoglobin reflective of a clinically relevant difference in GI toxicity between celecoxib and comparator NSAIDs?
4. Do the data support a clinically important difference between celecoxib and comparator NSAIDs in terms of renal adverse events?
5. Is there evidence to suggest an increase in cardiovascular thromboembolic events associated with celecoxib versus comparator NSAIDs?

To facilitate this discussion, we have attached a draft version of the slides that we intend to show at the Advisory Committee meeting.

As outlined in these slides, we believe that the 6 months analysis of symptomatic ulcers and/or ulcer complications is the least biased analysis of the study results, and that the use of aspirin is an important confounding variable. We also believe that the observed incidence rates of symptomatic ulcers and/or ulcer complications for diclofenac are underestimated because of withdrawals for GI intolerance. We would appreciate the agency's feedback on these conclusions.

DUPLICATE

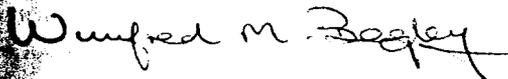
Due to the complexity of the statistical analyses associated with the GI outcomes of the study (notably adjustment for informative censoring), we would like to discuss with the agency the most appropriate way to address statistical issues that may arise during the committee meeting beforehand.

Further, we feel that the data indicate that celecoxib is associated with a diminished potential for chronic GI blood loss and renal toxicity compared to the NSAID comparators. Moreover, we see no signal indicating that there is an increase in cardiovascular thromboembolic events associated with celecoxib. We would accordingly solicit the agency's input regarding a discussion of these points as well as other issues that are of concern to the agency regarding the data submitted in the sNDA.

I have spoken previously with Dr. Goldkind and Dr. Kong regarding a telecon or meeting on this matter and January 26, 2001 has been set aside for a telecon with the FDA full team. Dr. Goldkind also offered me the possibility of a preliminary telecon the week of Jan 15 with Dr. Witter and himself. We would appreciate the preliminary telecon with Drs. Goldkind and Witter the week of Jan 15 and if possible a meeting rather than a telecon on January 26. Please could you confirm whether you are able to accommodate this request.

If you have any questions regarding this submission please contact the undersigned

Sincerely,

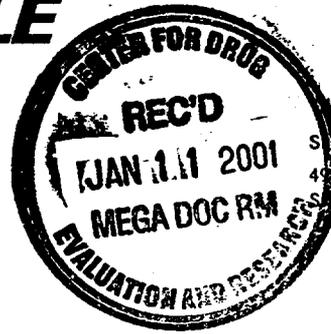


Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

Y. Kong Pharm. D.

WB/jr

SEARLE



SEARLE
45 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

January 10, 2001

Jonca Bull, 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

NEW CORRESP

Nc

588-009

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

Dear Dr. Bull,

With reference to your fax dated December 28, 2000 regarding our supplement S-009 we enclose a diskette with a TEXT table for all the narratives included in the Integrated Summary of Safety.

Please contact the undersigned if you require any further clarification.

Sincerely,

Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

cc: Y. Kong Pharm. D.

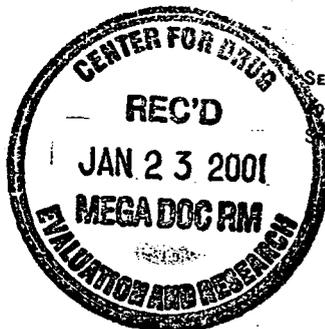
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ORIGINAL

SEARLE



SEARLE
901 SEARLE PARKWAY
ROCKFORD, ILLINOIS 60077

January 22, 2001

Jonca Bull, 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 SUPPL AMENDMENT
MR

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

528-009

Dear Dr. Bull,

Attached is the NDA archival copy of the letter that was sent to request a pre-meeting with Dr. Lin to discuss statistical aspects of the CLASS study prior to the Advisory Committee Meeting of February 7, 2001.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

cc: Y. Kong Pharm. D.

WB/jr

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ORIGINAL

SEARLE

January 22, 2001

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

Jonca Bull, 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



Celebrex® (celecoxib)
NDA 20.998 S-009

NEW CORRESP

Dear Dr. Bull,

Attached are the attendee list and the draft agenda for our meeting on Jan 26, 2001 as e-mailed to Dr. Y Kong on Friday, January 19, 2001.

SE8-009/NC

Please contact me if you wish to add or change the agenda.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

cc: Y. Kong Pharm. D.

WB/jr

SEARLE

SE8-009/NC



MARKWAY
MOIS 60077

January 23, 2001

Donna Bull, 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)
201 Corporate Boulevard
Rockville, MD 20850

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

Dear Dr. Bull,

Enclosed is our response to your fax dated January 18, 2001.

Please contact the undersigned if you require any further clarification.

Sincerely,

Vinifred M. Begley

Vinifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

BEST POSSIBLE COPY

cc: Y. Kong Pharm. D.

WB/jr

ORIGINAL

SEARLE

SE8/SE8-009/NC

1

January 24, 2001

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

Jonca Bull, 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



2

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

Dear Dr. Bull,

Enclosed is our response to your fax dated January 23, 2001 requesting a list of all subjects with GI symptoms that went on to have CSUGIE and GDUs.

We added some explanatory footnotes to Table 1.asa.dse so this copy differs from the cc-mail because of this.

Please contact the undersigned if you require any further clarification.

Sincerely,

Winifred M. Begley

Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

cc: Y. Kong Pharm. D.

WB/jr

ORIGINAL

SEARLE

January 31, 2001

Jonca Bull, M.D., Director
Division of Anti-inflammatory, Analgesic
and Ophthalmologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research (HFD-5)
9201 Corporate Boulevard
Rockville, MD 20850



SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

NEW CORRESP

NC

SEP-009

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

Dear Dr. Bull,

Based on the agreement in the pre-Advisory Committee Meeting between FDA and Searle/Pharmacia on January 26, both the ulcer complication and the ulcer complication/symptomatic ulcer will be presented as clinically meaningful endpoints. To ensure the robustness (1) of the p-values on complication/ulcer, we have performed some additional statistical tests using alternate survival analysis methods. The results have shown that the conclusions of the statistical analyses based on the Log-rank method do not vary based on use of different testing procedures or modeling with or without risk factors.

For ulcer complication/symptomatic ulcer on the ITT dataset, the methods we have employed include Log-rank, Wilcoxon, and Cox-regression. In addition to the treatment factor, the risk factors include age, history of GD ulcer, history of GI bleeding, CV disease and ASA use.

The same tests were also performed for ulcer complications on the non-ASA patient population since a significant difference for celecoxib vs. Ibuprofen was observed. The risk factors noted above (except ASA use) were included in the Cox-regression model. Enclosed please find the SAS outputs. All were generated by — SAS —

(1) A comment has been made by some consulting statisticians that the words "sensitivity analysis" may not be appropriate in this context. We would suggest we refer to it the analysis to assess the robustness of the p-values.

NDA 20-998
01/31/01
Page # 2

ITT – Ulcer Complication / Symptomatic Ulcer

Celecoxib vs Ibuprofen

Log-Rank	Wilcoxon	Cox Reg
0.017	0.011	0.005

Celecoxib vs NSAIDS

Log-Rank	Wilcoxon	Cox Reg
0.040	0.028	0.017

NON – ASA: Ulcer Complication

Celecoxib vs Ibuprofen

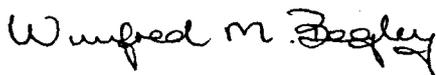
Log-Rank	Wilcoxon	Cox Reg
0.037	0.015	0.038

Note: Cox regression included factors: treatment, age, hx of GD ulcer, hx of GI bleeding, and CV disease. Plus ASA use for ITT cohort.

These data were sent via cc:mail to Dr. Y. Kong for forwarding to FDA statisticians. Our statisticians plan to call the FDA statisticians to review this package.

Please contact the undersigned if you require any further clarification.

Sincerely,



Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

cc: Y. Kong Pharm. D.

WB/jr

**APPEARS THIS WAY
ON ORIGINAL**

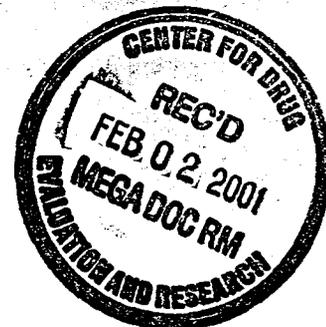
SEARLE

SEB-009/C

February 1, 2001

Jonca Bull, 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

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077



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

Dear Dr. Bull,

Enclosed is our response to your fax dated January 9, 2001 with questions from your pharmacokinetics reviewer.

Please do not hesitate to contact me if you require any further clarification.

Sincerely,

A handwritten signature in cursive script that reads "Winifred M. Begley".

Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

cc: Y. Kong Pharm. D.

WB/jr

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SEARLE

SE8-009/NC

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

February 1, 2001

Jonca Bull, M.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: **Celebrex® (celecoxib)**
NDA 20-998 S/009

Dear Dr. Bull:

Please find attached minutes from our January 26, 2001 meeting. If you have any questions please contact the undersigned.

Sincerely,

Handwritten signature of Winifred M. Begley.

Winifred M. Begley
Senior Director
Worldwide Regulatory Affairs
(847) 982-8155
(847) 982-8090 (fax)

Enclosures
WMB/res

ORIGINAL

SEARLE

SE8-009/NC

February 2, 2001

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

Jonca Bull, 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



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

Dear Dr. Bull,

At the Jan 26, 2001 meeting a question was asked regarding clarification of the number of deaths in the CLASS trial. The attached response addresses this.

Please do not hesitate to contact me if you require any further clarification.

Kind regards,

A handwritten signature in cursive script, appearing to read "Winifred M. Begley".

Winifred M. Begley
Senior Director
Regulatory Affairs
(847) 982-8155
(847)-982-8090

cc: Y. Kong Pharm. D.

WB/jr

SEARLE

NEW CORRESP
NC

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

February 14, 2001

Jonca Bull, 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



Celebrex® (celecoxib)
NDA 20-998

Dear Dr. Bull,

As requested, by Yoon Kong on February 9, 2001, enclosed is an updated Debarment Statement for the Supplemental NDA for Celebrex® NDA 20-998 submitted on December 18, 2000.

Should you have any questions regarding the content of the SNDA, please contact the undersigned at (847)-982-8980 or (847)-982-8090 (fax).

Sincerely,

A handwritten signature in cursive script, appearing to read 'Eva Essig'.

Eva Essig Ph.D.
Associate Director
Regulatory Affairs
(847) 982-8980
fax (847) 982-8090

cc: Y. Kong Pharm. D.

EE/jr

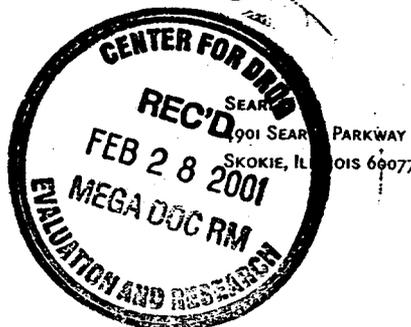
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SEARLE

358-0091E



February 27, 2001

Jonca Bull, 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

Celebrex® (celecoxib)
NDA 20-998

Dear Dr. Bull,

On June 12, 2001, Searle submitted a Supplemental New Drug Application (sNDA; S-009) to request modifications to the Celebrex labeling based on results of the Celecoxib Long-Term Arthritis Safety Study (CLASS). The conclusions from this study, emphasized in this sNDA, were based on the 6 month analysis of the primary study endpoint of ulcer complications due to the confounding issue of informative censoring which invalidated the data analysis for the entire study duration. The Advisory Committee briefing package prepared by Searle reflected this focus on the 6 month data analysis.

Since the time of this submission and receipt of the FDA review document, we have reconsidered our focus on the 6 month data analysis. It is clear that given the change in medical practice and the increase of "for cause" endoscopies, the ulcer complication endpoint alone was not the most clinically appropriate endpoint to assess serious UGI toxicity for the entire CLASS study. Instead, the study revealed that the expanded endpoint of ulcer complications and symptomatic ulcers, each prespecified in the study protocol, is a more clinically appropriate endpoint as it reflects medical practice, avoids much of the bias introduced by informative censoring and thereby considers the entire study data.

At a meeting with FDA on January 26, 2001, we discussed using the entire study data and reached agreement on the validity of this expanded endpoint. Subsequently, entire study data was presented at the Arthritis Advisory Committee Meeting on February 7, 2001.

In order to document this, we now submit a CLASS summary document, which provides the rationale for the data analysis. We hope that it will be beneficial to the review team and look forward to receiving any feedback you have on this summary.

FDA02272001.doc

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ORIGINAL

NDA 29-998 S/009

2/27/2001

Page 2

ATTENTION TO

From discussions with Dr. Kong, we understand that the review team intends on conducting labeling negotiations prior to taking an action at the primary user fee goal of April 12. We look forward to the initiation of these discussions with FDA in the next few weeks with a view to arriving at mutually agreeable labeling text by April 12.

Sincerely,

Winfred M. Begley

Eva Essig Ph.D.
Associate Director
Regulatory Affairs
(847) 982-8980
fax (847) 982-8090

cc: Y. Kong Pharm. D.

EE/jr

APPEARS THIS WAY
ON ORIGINAL

SEARLE

NEW COPY

NC

March 15, 2001

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

Yoon Kong, Pharm.D.
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

SEB-009(C)

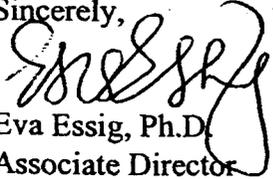
Celebrex® (celecoxib)
NDA 20-998 / 5-009

Dear Dr. Kong,

On Tuesday, March 13, we electronically transmitted the revised draft label for CLASS as a Word document entitled "13Mar01CLASStoFDA". We now provide the requested three diskettes and hard copy of the labeling. This version has been renamed "15Mar01CLASStoFDA" since a minor change has been made; in Figure 3 (Page 9) the p value has been changed to $p=0.05$.

We look forward to beginning labeling negotiations with FDA

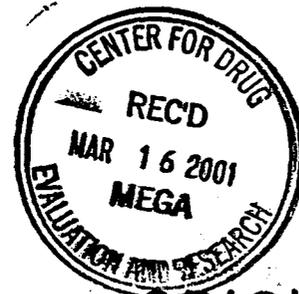
Sincerely,


Eva Essig, Ph.D.
Associate Director
Regulatory Affairs
(847) 982-8980
Fax (847) 982-8090

Attachments
EE/jr

FDA031501.doc

a MONSANTO  company



ORIGINAL

SEARLE

NDA SUPPL AMENDMENT

SE8-009/NC

March 26, 2001

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

Jonca Bull, 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



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

Dear Dr. Bull,

Enclosed is our response to Dr. Witter request for information regarding the mean and median time of exposure (with 95% CI) for the three treatments in CLASS.

Please do not hesitate to contact me if you require any further clarification.

Kind regards,

A handwritten signature in cursive script, appearing to read "Eva Essig".

Eva Essig, Ph.D.
Associate Director
Regulatory Affairs
(847) 982-8980
(847) 982-8090 (Fax)

Attachments
EE/jr

ORIGINAL

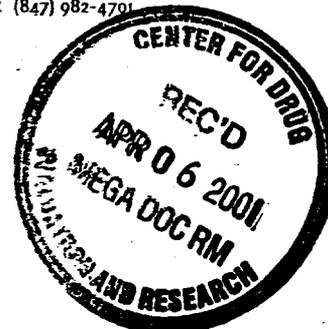
SEARLE

SE8-009/S4
3

April 4, 2001

Jonca Bull, M.D., Acting 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 Blvd.
Rockville, MD 20850

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



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

Dear Dr. Bull:

Please refer to our Supplementary New Drug Application for Celebrex capsules which was submitted on June 12, 2000.

We acknowledge that we did not provide, in compliance with CFR 314.50 (d) (5) (vi) (b), a "safety update report" for this submission. The CLASS trial, the subject of the SNDA, was complete at the time of submission with no patients continuing treatment. Therefore there were no additional data from this trial to be reported in a safety update. We recognize, however, that a safety update is expected to address new safety information from all sources. To this end, I enclose a copy of the Integrated Summary of Safety (Document N49-00-07-834), which was submitted with the subsequent SNDA (S/010) for the "management of pain" indication on December 18, 2000. This report included an update of the safety data for celecoxib through the end of September 2000.

If there is anything further that is needed regarding this question, please do not hesitate to contact the undersigned.

Sincerely,

Joc: Eva Essig, Ph.D.
Associate Director,
Regulatory Affairs
Tel: (847) 982-8980
Fax: (847) 982-8090
Enclosure

cc: Y. Kong, Pharm. D.

ORIGINAL

SEARLE

SE8-009/NC
NDA SUPPL AMENDMENT

April 4, 2001

Jonca Bull, 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



SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

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

Dear Dr. Bull,

With reference to your fax dated January 9, 2001 regarding our supplement S-009 we enclosed the response to your question on diclofenac

Please contact the undersigned if you require any further clarification.

Sincerely,

Eva Essig, Ph.D.
Associate Director
Regulatory Affairs
(847) 982-8980
(847) 982-8090 (Fax)

Attachments
EE/jr

CC: Y. Kong

FDAClass04042001.doc

a MONSANTO  company

ORIGINAL

TELECON MINUTES

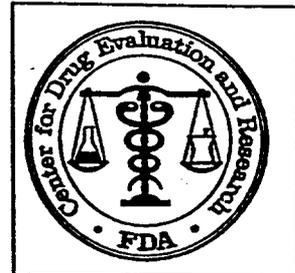
Meeting Date: April 3, 1998

NDA/IND: —

Drug Name: COX-2

Sponsor: Searle

Type of Meeting: Telecon to discuss the CLASS protocol



Attendees: _____ **Title:** _____

FDA

Michael Weintraub, M.D.	Director (Acting)
John E. Hyde, M.D.	Deputy Director
James Witter, M.D.	Medical Officer
Chin Koerner, M.S.	Regulatory Health Project Manager
Lillian Patrician, M.S.	Statistician
John Senior, M.D.	Medical Officer

Searle

J. Alexander
W. Begley
a. Burr
S. Geis
D. JordanR. Spivey
K. Verburg
W. Zhao

Pfizer

J. Finman
R. Folger
L. Loose

Background:

The initial meeting where a study to look at clinical outcomes to modify the GI Warning section of the NSAID labeling was on October 22, 1997. Subsequently, a preliminary protocol was submitted and a telecon on January 15, 1998 took place. This was followed by a final draft of the protocol. Today's telecon is to provide Divisional recommendations on the final draft of the protocol.

Minutes

1. Question: Does the FDA agree that the doses selected for the NSAID comparators and cox-2 are appropriate.

Response: The doses are appropriate. But the Division would like to see _____ bid to ensure blinding. Additionally, the Division would like to see samples of the product and dummies. The Division would also recommend _____

2. Question: Does the FDA agree that the definitions of clinically significant upper gastrointestinal events as outlined in the protocol are appropriate?

Response: See attached memo from Dr. John Senior.

3. Question: Does the FDA agree that the primary outcome variable is clinically significant UGI event as a composite measurement?

Response: yes. As secondary endpoints, the sponsor should capture presumptive and probable events for assessment and categorization.

4. Question: Does the FDA agree the primary statistical comparison for this study is cox-2 against the NSAIDs as a group?

Response: yes, even though NSAIDs do not all have the same rate of ulcers. See additional comments under question 10.

5. Question: What is the required follow up period for patients who withdraw early from the study?

Response: Minimally the sponsor should have a 60 day follow up to collect as much safety data as possible. Additionally, the Division recommends some continued follow up until the end of the 52 week period.

6. Question: How should we analyze any clinically significant UGI events that occur after discontinuation from the study?

Response: The primary analysis should be for event during the study; Time to Event while on the blinded drug. A secondary analysis should be for an Intent to Treat followed for 52 weeks.

7. Question: At the FDA'S request, we intend to allow 1000 patients to continue the study for one year. Does the FDA agree that the 1000 patients include cox-2 and NSAID treated patients.

April 3, 1998 telecon

Page 3

Response: All patients will be exposed for at least 6 months and 2000 patients will be exposed for 12 months with 1000 patients on cox-2 and 1000 patients on other NSAIDs.

8. Question: We propose to write and submit a report once the time to UGI event analysis associated with cox-2 to that of NSAID therapy.

Please consider the following: the length of the study will be influenced by the time required to achieve the expected number of clinically significant UGI events. If enrollment is rapid then the time required to achieve the expected number of UGI events may be short. Consequently, this would result in stopping this phase of the study before a number of patients complete 6 months of treatment.

Response: The Division is interested in the length of exposure as well as the number of events. The Division recommends that the proposed length of study be completed. The Division cannot endorse this analysis.

9. Question: We propose to _____

Response: We will accept a report any time and any amendments thereafter. The Division may not be able to make a final recommendation for the SNDA until all the information has been reviewed.

10. Question: Assuming a positive result in this study, we understand from previous discussions that we will be able to claim superiority against each NSAID studied. (Ibuprofen, diclofenac and naproxen).

Response: If the analysis is cox-2 compared to pooled data collected from all three NSAIDs then the sponsor will not be able to claim superiority against each NSAID studied. However, if the data is supportive, a modification to the GI Warning section may be possible.

In past conversations where a claim against each comparator was discussed, the study design was different (endoscopic) and the statistical analysis did not allow for pooling of the comparator data.

Additional comments:

The Division recommends that a serology screening for H. Pylori be conducted at the beginning of the study and a breath test for H. Pylori be conducted at the end of the study. The investigator should be kept blind of the results.

The Division recommends that a bone safety study be conducted at some point in the drug development program. Bone density, urine and serum markers should be monitored.

Memo

Comments from Dr. John Senior regarding _____ CLASS protocol. These comments are a follow-up to the telecon of April 3, 1998 between the Division and Searle.

... simply wanted to emphasize the clear definition of the major endpoints of perforation, obstruction, and significant ulcer bleeding. Also to be captured are the bleeding episodes that are clinically significant in terms of volume loss, drop in Hb/Hct, postural hypotension, need for 2 or more units of packed rbc - but without an ulcer or defined bleeding site; and the ulcers found that are not complicated by P/O/UB.

... the easiest is perforation, which requires some sort of surgical intervention, either by laparotomy or laparoscopy to close the hole, and this must be documented and is easy to assess.

... next is obstruction, which should be diagnosed by symptoms of vomiting, gastric dilatation on x-ray, poor emptying by a variety of methods such as _____, gastric retention of fluid by aspiration, then medical intervention by NG intubation and IV fluids, plus some sort of surgical intervention to fix it by some means including a pyloroplasty, endoscopic dilatation, etc.

... most difficult to define is bleeding, that comes in all sizes and colors from red to black. To be included in an NSAID-induced ulcer bleeding of clinically significant magnitude as a life threatening complication, there needs to be evidence of a gastroduodenal ulcer or bleeding lesion; hematemesis/melena/visible bleeding OR heme+ aspirate/stool with _____ in Hb by atleast 1.5 g/dL/decrease in Hct by at least 0.05/postural hypotension (all after reasonable rehydration. Decision to hospitalize and transfuse with 2 or more units of packed RBC would be very strong confirming evidence. This is a clinical judgment as to when the bleeding is "significant" and not just heme+ stool without any defined bleeding site in the GI tract.

... separate classifications of gastroduodenal ulcer without significant bleeding, and bleeding without gastroduodenal ulcer should be recorded and tabulated, but not necessarily lumped in with serious NSAID-induced complications that need to be minimized by better anti-inflammatory agents than the conventional class of NSAIDs.

... it is very important that all study participants know exactly what to do, what data to gather, whenever a suspected problem arises. I am not sure that the protocol addresses this sufficiently, and it should be reiterated in the Investigators' Brochure and in the Case Report Forms, as well as in the instructions to patients, the Consent Form, and in the important Investigators' meetings to be held (I hope) by the company. We learned from MUCOSA that it is not enough for practitioners just to do whatever they do, but to realize they are part of an important data gathering study.

... I wanted to emphasize that they should tighten up the protocol to include doing sitting and standing BP and pulse, and stool/rectal heme testing at every visit. They should as well as describe in the protocol exactly what is expected of the practitioner who finds a "suspicious agent" in a patient on study. This should spell out the data to be collected, such as endoscopy reports and pictures, the serial values of Hb/Hct, all procedures done, emergency room/hospital admission records, operative reports, discharge summaries, autopsy reports - in fact the whole medical record if possible.

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Date: September 22, 1998

IND _____

Sponsor: Searle

Subject: CLASS 1 and 2 Studies

Related submission: August 27, 1998 SN 355

Background:

The purpose of this telecon will be convey guidance and concerns to Searle regarding their GI Outcomes Studies, CLASS 1 submitted on August 27, 1998, and CLASS 2, still to be submitted to the Division for review.

I. General comments on the proposed protocol:

- 2.2. 5 The Division recommends that alcohol, tobacco and low dose ASA (under 326 mg) use be added to the list of potential risk factors to be evaluated. These should be historically quantitated to the extent possible such as, repeat questioning at each follow-up visit (packs per day for tobacco and alcohol containing beverages per day for alcohol)
- 3.2.c Please specify what "active GI disease" is referring to.
- 4.1 The Division recommends that clinical lab tests include serum ferritin, iron, iron binding capacity, and mean corpuscular hemoglobin as a means to evaluate chronic blood loss. Please propose criteria for meaningful clinical change in these parameters.
- The Division may be requesting additional renal safety information. It may be helpful to incorporate renal lab tests into the CLASS protocols.
- 4.2.a .7 The Division recommends that definition of cardiovascular disease as risk factors be more defined.
- 4.2.a.11, 12. Please see above 2.2.5 for clarification.
- 4.3.b.2 Please explain "short term antacids therapy". How many short courses of antacid therapy will be allowed.
- 4.3.b.4 Please specify in what way the interim FOBT will be analysed or impact on the decision to endoscope.
- 4.4a, b, c The Division requests that videos be made of all endoscopies to better document the GI events.
- 5.4 The Division recommends that Searle monitors and staff should be blinded as well.

5.5 The Division recommends that events occurring 1-2 weeks after final visit be noted and recorded.

II. Comments on the definition of Primary Endpoints for major (serious) or clinically relevant UGI events in clinical trials.

The Division recommends the following to be primary endpoints. It is acceptable to also include the broader defined endpoints as proposed by the sponsor as either secondary or co-primary endpoints. The statistical criteria for success remains to be discussed.

Perforation

Perforated ulcer proved at surgery: exclude malignant ulcer, (if clinical information is available to suggest foreign body perforation, or other causes-exclude). ~~If small bowel or large bowel perforation with pathology consistent with NSAID and not consistent with ischemia, obstructive, inflammatory bowel diseases related, diverticular or other potential causes, consider NSAID related.~~

Gastric outlet obstruction:

Caused by endoscopically proven ulceration and narrowing in the antral and pyloric area (not related to malignancy or extrinsic compression) in association with symptoms of nausea and vomiting lasting over 24 hours and requiring hospitalization. Initial UGI contrast study revealing gastric outlet obstruction (not gastroparesis or generalized ileus) ultimately shown to be related to ulcer or benign stricture also acceptable.

UGI bleeding

The presence of hematemesis or gross blood (not blood streaked gastric contents) on NG lavage or, melena, hematochezia in addition to the identification of an UGI tract lesion

as defined below and one of the following:

- a. drop in hemoglobin (Hgb) of 2gm or more with adequate hydration. If urgent transfusion is required before Hgb can equilibrate, final Hgb equal to or lower than pre-bleed Hgb.
- b. Hypotension or orthostatic hypotension: Systolic BP 20mm Hg. below pre-bleed baseline or systolic BP under 100 plus pulse rate over 100 or >20 point drop in systolic BP when moving from lying to standing or sitting.

Localization of any major acute gastrointestinal bleeding is important.

Upper gastrointestinal bleeding indicates hematemesis, hematochezia or melena with documented upper GI source and no known LGI source by endoscopy. The

Localization of any major acute gastrointestinal bleeding is important. Upper gastrointestinal bleeding indicates hematemesis, hematochezia or melena with documented upper GI source and no known LGI source by endoscopy. The identification of an UGI tract lesion as the source of GI bleeding requires the presence of an endoscopically confirmed ulcer, erosions, hemorrhagic mucosal changes, vascular lesion, mucosal tear or varices along with an evaluation of the LGI tract as noted below. (Table will be distributed at the meeting, I cannot send it electronically)

A positive colonoscopy or Barium enema indicates a site of active bleeding in the colon or terminal ileum. This includes active colitis, ulcerated neoplasm, AVM, hemorrhoids or actively bleeding diverticulae. Non-ulcerated or eroded mass lesions or polyps and non-bleeding diverticulae should be considered negative.

III. Comments on the Statistical Analysis Plan:

The Division recommends that the studies be sufficiently powered to detect differences between celecoxib and each of the active comparators. It is acceptable to pool CLASS 1 and CLASS 2 data for the celecoxib arm.

The Division would not allow comparative claims to be based on pooled data.

IV. Comments on the Proposed Interim Analysis:

Please provide further clarification the basis on which the DSMB would make the determination that an interim analysis should be conducted for purposed of stopping the study.

The Division recommends that a minimum of 6 months completion for each patient be attained, before an interim analysis is to be considered by the DSMB.

**APPEARS THIS WAY
ON ORIGINAL**

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weeks after they complete participation in the study but simply report the information if it comes to our attention.

- II. Response to comments on the definition of Primary Endpoints for major (serious) or clinically relevant UGI events in clinical trials.

We would respectfully take issue with the Agency's definitions of serious UGI events. Specifically, the proposed endpoints:

1. mix together UGI and LGI events (e.g. perforations);
2. do not allow for the inclusion of significant bleeding events that are halted by medical intervention in a timely fashion;
3. do not take into account physiologic variation in the adaptation to bleeding in terms of maintenance of hematocrit or cardiovascular reflexes; and
4. appear to require upper and lower endoscopies in patients with events.

Moreover, the 2-4% event rate cited in current FDA NSAID class labeling (perforations, obstruction, UGI bleeding and symptomatic ulcers) is consistent with the event rates observed in the MUCOSA study and other studies in the literature which use definitions of events similar to that proposed for the -035 study. To change these definitions will create an inconsistency in event reporting between this study and the published literature and current labeling.

**APPEARS THIS WAY
ON ORIGINAL**

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9/22-98
9/22-98
11/22/98

Telecon Minutes

September 22, 1998
Searle
IND
CLASS 1 and 2

Present: Bob Delap, John Hyde, Jim Witter, Vickey Lutwak, Chin Koerner, Stan Lin, Laura Lu

Sponsor: Winifred Begley et al

Minutes:

The discussion with the sponsor was mostly statistical in nature. We did not have the necessary clinical reviewers there to discuss the GI endpoint definitions.

The sponsor was asked to think through statistical adjustments necessary for using and winning against three comparators. Would they need to win against all three, two out of three, or any one comparator in order to make a superiority claim.

The sponsor was also asked to think through the interim analysis as it would be used in CLASS 1 and 2, now that there are two instead of one study.

Action:

There will be another internal meeting to discuss endpoints as they relay to claims.

There will be another telecon with the sponsor.

Submitted by

CS

9/22/98

Chin Koerner, Project Manager

cc:

Div Files
HFD-550/Lutwak