Telecon Minutes/Fax to Sponsor
Date: September 22, 1998

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.

The comments found in these minutes were faxed to the sponsor prior to the telecon, but not all comments were discussed (see minutes).

Minutes:
Attached

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 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.

DIV I/C

SPONSOR MEETING MINUTES

Meeting Date: October 2, 1998

IND/NDA: ———

Drug Name: Celecoxib (SC-58635)

Sponsor: G. D. Searle

Type of Meeting: Teleconference CLASS study -035

FDA Attendees:
B. DeLap, J. Hyde, J.Witter, L. Goldkind, S. Lin, M. Averbuch, C. Fang, V. Lutwak
Searle: W. Begley, A. Burr, S. Geis, D.Jordan, J.Lefkowith, R. Spivery,W.Zhao, F. Silvestein,
Pfizer: E. Forster, L.Loose, R.Folger, M.Fletcher, J.Finman

Re: Searle's General Correspondence dated August 27, 1998, and GS dated September 29, 1998 (attached).

Summary:
Searle's introductory comments were made by S. Geis and followed by F. Silverstein's presentation on primary endpoints, UGI bleeding. Larry Goldkind noted that analysis of the MUCOSA study were complicated by a lack of precision in UGI bleeding endpoints. After some discussion about endpoints, Bob DeLap suggested that the endpoints could possibly be looked at in two ways: 1.) A broader definition, as outlined in Searle's protocol, submitted on August 27, 1998, and 2.) as outlined with the Division's recommended UGI bleeding endpoints which are more strictly defined.

Clarification on the following point to Searle's response to the division's general comments on the proposed protocol and GS dated September 29, 1998 (attached).

2.25 Agree. Aspirin will be added. In addition, it was pointed out that usage may change over time; it is desirable to collect usage information during/after the study, as well as at baseline.
3.2.c Accept, more examples to be added.
4.1 It is important to have baseline values for all patients, for comparison to follow-up values obtained in patients with evidence of bleeding.. For the renal safety, it was suggested to collect in addition to BUN and Crt, Bicarb, Phosphate. Thus, all patients should have serum ferritin, iron, iron binding capacity, and mean corpuscular hemoglobin at baseline. Follow-up studies are not needed if there is no evidence of blood loss.
4.2.a.7. Sponsor will list CV risk factors in the protocol.
4.3.b.2. The sponsor agreed to provide a stricter definition for antacid use to control as best possible, and will record use of antacids by patients during the study.
4.3.b.4. The sponsor claimed that video equipment may not always be available to record

endoscopy studies but would make an effort to cooperate with this request.
5.4. Clarification was made that all the committees and Searle's staff are blinded.

Page 2

5.5
Searle's overall plan regarding collection and analysis of AEs occurring during the study and after study completion are acceptable (see attaached).

The Division recommends that events occurring 1-2 weeks after the final visit be noted and recorded. Analyses with/without these events might be performed.

Interim Analysis:
Searle was to consider the multiple-endpoints (i.e., co-primaries) and multiple treatment group comparison issues in the studies. In addition, interim analysis might be conducted after each patient had at lest a six-month follow-up. Searle was to provide details and statistical plans to these issues.

Action Items:

- Larry Goldkind will provide a revised table for "Examination of the Upper or Lower GI Tract" and recommended revised wording for the work-up for hematemesis or melena in Appendix 1,
  page 5 of 6.
- John Hyde will provided a copy of D Throckmorton's proposal regarding the lab tests needed to evaluate renal safety.

cc:
IND
Div.File
HDF-105/ DeLap
HFD-550/ Hyde/Witter/St Lin/Averbush/ Fang/ Villalba
HFD-550 / CSO/ VLutwak

TELECON MINUTES

TELECON DATE: January 25, 2001 **TIME:** 3-3:20 p.m. **LOCATION:** CORP S300

NDA: 20-998/S-009 **Telecon Request Submission Date:** January 22, 2001

DRUG: Celebrex (celecoxib)

APPLICANT: Searle

TYPE of TELECON: Guidance

FDA PARTICIPANTS:

Lawrence Goldkind, M.D.	Clinical Team Leader
Laura Lu, Ph.D.	Statistics Reviewer
Stan Lin, Ph.D.	Statistics Team Leader

INDUSTRY PARTICIPANTS:

Searle/Pfizer

William Zhao, Ph.D.	Director, Clinical Statistics
Steve Geis, Ph.D., M.D.	Vice-President, Arthritis Clinical Research
Jim Lefkowith, M.D.	Senior Director, Arthritis Clinical Research
Ken Verburg, Ph.D.	Senior Director, Arthritis Clinical Research
Aziz Karim, Ph.D.	Director, Senior Scientific Advisor- Biopharmaceutics
Dave Jordan	
Clem Maurath	
Eva Essig, Ph.D.	Associate Director, Regulatory Affairs
Winifred M. Begley	Senior Director, Regulatory Affairs

Pfizer

Gordon Lan, Ph.D.	Distinguished Scientist Statistics Research
Mona Wahba, M.D.	Senior Associate Director, Clinical Development
Jeff Finman	

Consultant

TELECON OBJECTIVES: To provide clarification to sponsor's queries regarding queries and concerns as detailed in the June 22, 2001, meeting request prior to the Advisory Committee Meeting of February 7, 2001.

BACKGROUND INFORMATION:
This teleconference was requested by sponsor to discuss and clarify statistical issues regarding the data generated from sponsor's Celecoxib Long-Term Arthritis Safety Study (CLASS) in anticipation/preparation for the Advisory Committee meeting scheduled for February 7, 2001. Specific items to be discussed are outlined in the sponsor's meeting request letter dated June 22, 2001.

DISCUSSION:
Per sponsor's meeting request letter:

> *"We have received a copy of the FDA reviewer's comments that have been sent to the Arthritis Advisory Committee for the February 7 meeting. We notice that there is a misunderstanding of the date assigned to a GI event, which may have masked the informative censoring, caused by withdrawal due to GI symptoms. The GI event data was assigned retrospectively by the committee as the date of the first sign or symptom of the event. If this was a GI symptom, then the date of the event and the AE are identical by definition. This convention may not have been clearly stated in the report thus leading to confusion. Given this convention, it is distinctly possible that had these patients exited the study at the date of the GI symptom, an ulcer complication would not have occurred or would have been missed due to lack of subsequent information. This is a critical misunderstanding since the reviewers have assumed that if the symptom dates and event dates are the same, there would have been no events missed due to GI AE withdrawals."*

FDA indicated that they understood that gastrointestinal (GI) adverse events followed a CSUGIE and that there was lag time involved from the time patient was identified with the GI symptoms and with the actual GI outcome.

Sponsor agreed that possibly the GI symptoms preceded bleeding by a sufficient period of time for informative censoring to occur within this database.

FDA noted that in some cases, the relationship between the GI symptoms and events were clearly delineated. Hence, FDA suggested that there was no clear basis for stating that informative censoring existed in this study. FDA further stated that this database did not support the CLASS trial with respect to its primary clinical endpoints.

Sponsor pointed that they exercised informative censoring in this trial when dealing with GI events by reporting any gastroduoenal ulcers (GDUs) and CSUGIEs.

FDA agreed that informative censoring is possible, however, in this particular trial in RCTs, this was not identified.

FDA stated that the most valid way to capture any potential informative censoring would be to use the CSUGIE/GDU endpoints.

Sponsor indicated that clinically meaningful analysis was performed, however, not on the pre-specified endpoints designated in the protocol. Further, sponsor inquired if this is a meaningful endpoint. How to apply statistical analysis to this *post hoc* endpoint is problematic.

Sponsor and FDA agreed to pursue dialogue to work in concert to prepare for the Advisory Committee meeting and on the sNDA.

At the adjournment of this teleconference, FDA reminded the sponsor that the purpose of tomorrow's pre-Advisory Committee meeting with the sponsor would be to work jointly to make the February 7, 2001 Advisory Committee meeting a successful means of presenting scientific information regarding the results of the CLASS study to the public as well as medical community.

ACTION ITEMS:

1. FDA will convey minutes of the teleconference to sponsor.

_____
Yoon Kong, Pharm.D.
Project Manager

Concur:_____
Lawrence Goldkind, M.D.
Clinical Team Leader

TELECON MINUTES

/s/

Lawrence Goldkind
3/4/01 01:18:29 PM

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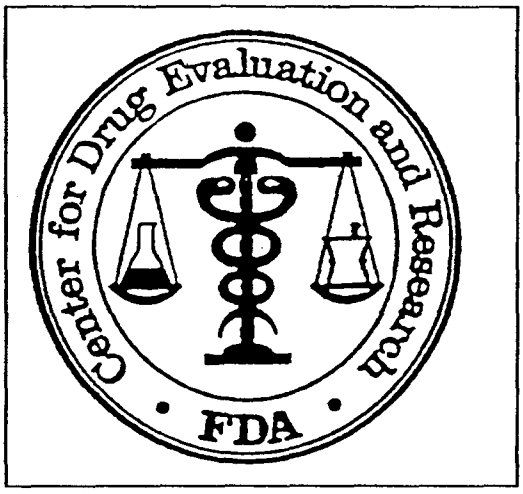

From: Yoon Kong, Pharm.D.

Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 8/03/00

To:

Name: Winifred M. Begley
Senior Director, Regulatory Affairs
Company: Searle
City: Skokie State: Illinois
Phone #: (847) 982-8155
FAX #: (847) 982-8090

Number of Pages (INCLUDING COVER PAGE): 3

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

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

Dear Winifred:

Please find attached our acknowledgement letter for this sNDA application.

Please give me a call if you have any questions or concerns.

Thank you.

/S/

Yoon Kong, Pharm.D.

faxed to sponsor on 8-3-00

cc: NDA 20-998
HFD-550/ Div. File
HFD-550/ Y. Kong

MESSAGE CONFIRMATION

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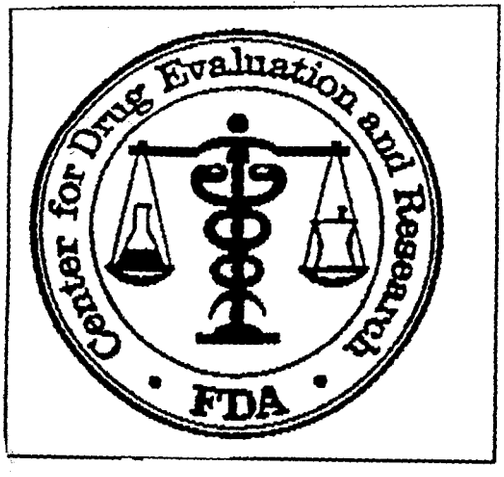

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-998/S-009

PRIOR APPROVAL SUPPLEMENT

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

AUG 0 3

Dear Ms. Begley:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Celebrex Capsules (celecoxib capsules), 100 mg and 200 mg

NDA Number: 20-998

Supplement Number: S-009

Therapeutic Classification: Standard (S)

Date of Supplement: June 12, 2000

Date of Receipt: June 14, 2000

This supplement proposes the following change(s): modifications to the **Warnings** and **Clinical Studies** sections of the labeling based on a large gastrointestinal outcome study.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 14, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 12, 2001 and the secondary user fee goal date will be June 12, 2001.

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Yoon J. Kong, Pharm.D., Regulatory Project Manager, at (301) 827-2090.

Sincerely,

/S/ for

Leslie Vaccari
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
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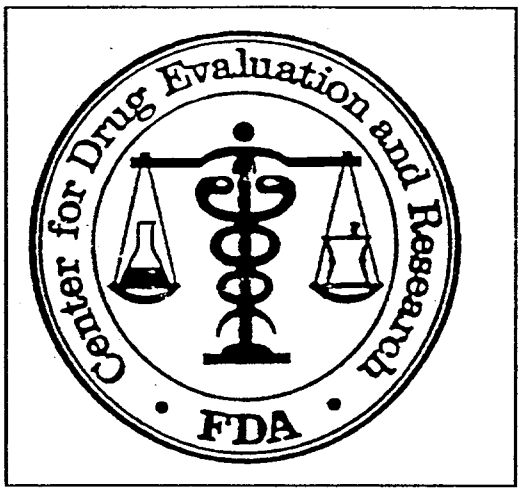

From: Yoon Kong, Pharm.D.

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 8/03/00

To:

Name: Winifred M. Begley
Senior Director, Regulatory Affairs
Company: Searle
City: Skokie State: Illinois
Phone #: (847) 982-8155
FAX #: (847) 982-8090

Number of Pages (INCLUDING COVER PAGE): 2

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

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

Dear Winifred:

Please find attached informational request from our statistical reviewer for this supplement application.

Please give me a call if you have any questions or concerns.

Thank you.

/S/ 8-3-00.
Yoon Kong, Pharm.D.

faxed to sponsor on 8-3-00.

cc: NDA 20-998
HFD-550/Div. Files
HFD-550/Y. Kong
HFD-725/Laura Lu

Statistics

Please provide the following information:

1. A SAS transport dataset for the ITT population including the following variables:

   Patient #, Study # , Center, Treatment Code, Demographics and Baseline Characters (including all risk factors evaluated), Patient Disposition (for AE withdrawal, separate those due to GI symptom from others), Time to CSUGI Event (days), Indicator for Censoring and Indicator for CSUGI Event, Time to Alternate CSUGI Event and Indicator for Censoring, Days on Treatment, Efficacy, QOL variables, and an Indicator for Investigators with Financial Interest Required Disclosure.

   Also, a hard copy of variable formats is also preferable.

2. Kaplan-Meier curves for CSUGI events for each of the three treatment groups during the entire study period.

MESSAGE CONFIRMATION

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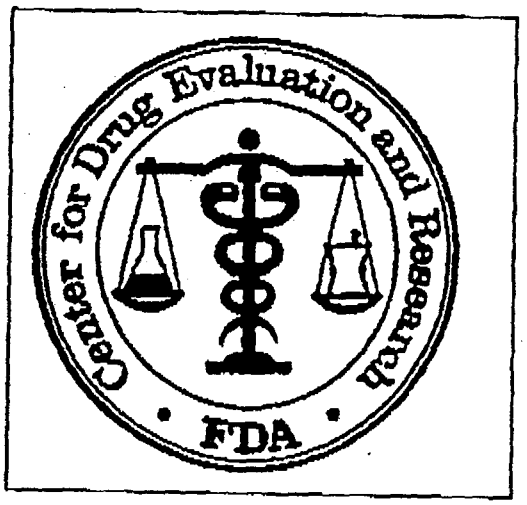

From: Yoon Kong, Pharm.D.

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 8/03/00

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Senior Director, Regulatory Affairs
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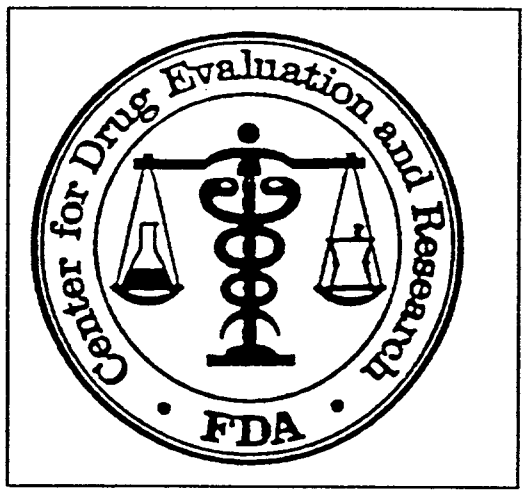

From: Yoon Kong, Pharm.D.

Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
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Date: 9/26/00

To:

Name: Winifred M. Begley
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Phone #: (847) 982-8155
FAX #: (847) 982-8090

Number of Pages (INCLUDING COVER PAGE): 2

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

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

Dear Winifred:

Please find attached clinical information request regarding this supplemental application.

Please give me a call if you have any questions or concerns.

Thank you.

/S/

Yoon Kong, Pharm.D.

faxed to sponsor on 9-26-00.

cc NDA 20-998/S-009
HFD-550/Div. File
HFD-550/L. Goldkind
HFD-550/Y. Kong

Clinical-CLASS Study

1. Please identify where in the submission, there is a summary of how subjects withdrawing due to GI AE's were clinically evaluated (other than those meeting the symptomatic definitions in the algorithm appearing in appendix 1).

2. What percent of subjects who withdrew due to GI symptoms were evaluated for ulcers in each group. Is there an analysis of this data?

3. Why is diarrhea included in the definition of a GI adverse event that is associated with CSUGIEs in the imputation analysis?

4. Where in the protocol was it prespecified that evaluation of dyspepsia, abdominal pain, and nausea and vomiting was "required"? See clinical assessments section of recent JAMA article on CLASS study. (Note: appendix 1 of protocol, section 1.6 entitled "Algorithm for work-up of suspected UGI events" states that **severe acute** abdominal pain and **intractable abdominal pain with** nausea and vomiting were the triggers for recommended work-up).

CONFIRMATION

09/26/00 08:40

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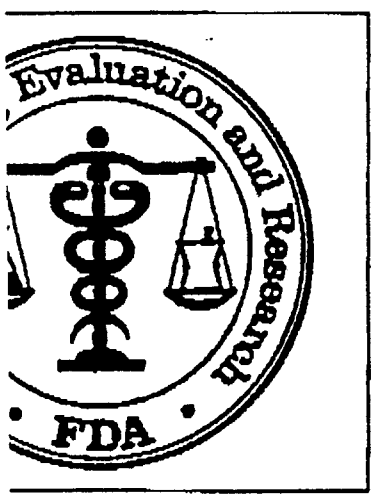

From: Yoon Kong, Pharm.D.

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
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Date: 9/26/00

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Fax

L. Vaccari

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Winifred Begley/Searle	From:	Leslie Vaccari
Fax:	847-982-8090	Fax:	301-827-2540
Phone:	847-982-8155	Phone:	301-827-2147
Pages:	4	Date:	August 29, 2000

Re: July 26, 2000 Meeting Minutes NDA 20-998

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

• **Comments:**

Attached are the Minutes for our 7-26-00 Meeting. I have not included the attachment because it is only a copy of the overheads that you used in the meeting and provided to us.

Leslie Vaccari

cc: Original NDA 20-998
HFD-550 / Div File
/ LVaccari
/ Yong

MEETING MINUTES

MEETING DATE: July 26, 2000 **Time: 1-3pm** **Location: Corp2**

NDA 20-998

Meeting Requested: 15 May 2000
Meeting Scheduled: 16 May 2000
Briefing Document Received: 30 June 2000

DRUG: Celebrex (celecoxib)

APPLICANT: Searle

TYPE of MEETING: Special (Discussion of CorrectRx Program Report)

FDA ATTENDEES:
Robert DeLap, M.D., Ph.D., Director Office of Drug Evaluation V
Karen Midthun, M.D., Division Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products
(Peter Honig, M.D., Director, Post-Marketing Drug Risk Assessment: Scheduled but unexpectedly unable to attend)
James Witter, M.D., Ph.D., Medical Officer
Mary Jane Walling, Associate Director Regulatory Affairs, ODE V
Julie Beitz, M.D., Director DDREI, OPDRA, CDER
Jerry Phillips, RPh., Associate Director, OPDRA
Carol Holquist, RPh., Safety Evaluator, OPDRA
Parivash Nourjah, Epidemiolgist, OPDRA
Renan Bonnel, RPh., Safety Evaluator, OPDRA
Leslie Vaccari, Supervisory Consumer Safety Officer

INDUSTRY ATTENDEES:
Richard Spivey, Sr. Vice President, Regulatory Affairs, Searle
Winifred Begley, Sr. Director Regulatory Affairs, Searle
Inga Feiter, Executive Director, Marketing Analytics, Searle
Susan Kundel, Sr. Director Celebrex Marketing, Searle
Amy Broidrick, Director, Celebrex Marketing, Searle
Stephen Glockenmeier, Associate Director U.S. Marketing, Searle
Joseph Papa, President U.S. Operations, Searle
Robert L. Bogomolny, General Counsel, Searle
Geoff Levitt, Venable, Searle Outside Counsel
G
J

Phyllis Christensen, Director, Regulatory Affairs, Pfizer

BACKGROUND:
On December 31,1998, Celebrex was approved for the relief of the signs and symptoms of osteoarthritis and adult rheumatoid arthritis. Celebrex was available in pharmacies on January 19,1999.

As of March 3, 1999, FDA had received a total of 52 adverse drug reactions involving Celebrex. On March 18, 1999, the FDA contacted Searle regarding the issue of name confusion and the medication errors due to the similarity of brand names among Celebrex (celecoxib capsules), Celexa (citalopram hydrobromide tablets) and Cerebryx (fosphenytoin sodium injection). A Dear Healthcare Professional Letter issued April 19, 1999 to alert the medical community of the problem. Also in response, Searle immediately began working with FDA to develop a comprehensive program which was subsequently named the "CorrectRx Program".

The CorrectRx Program had two main components:

1. An Educational Campaign to increase awareness among healthcare professionals about the issue of drug name confusion and reducing potential errors stemming from such confusion; and
2. The CorrectRx Survey, an evaluation component, to determine progress made by the CorrectRx Program and to assess awareness and reported behaviors among physicians, pharmacists/pharmacy technicians and nurses regarding the prescribing and dispensing of these products.

Today's meeting was prompted when the FDA (as suggested by OPDRA) requested Searle to present the CorrectRx Program Report when completed.

INTRODUCTIONS and PRESENTATION:
Following introductions, Searle presented an overview of the CorrectRx Program. Refer to attached copy of overheads used.

DISCUSSION:

The FDA noted that more medication errors have been reported on this product than any other. The FDA continues to have concerns. How much do we know about how many cases are actually occurring, how do we calculate what is the actual decrease in errors, and what part of this is due to the educational campaign? All agree that it may be positive that we don't have the same number of errors as at the time of launch but the FDA is not confident in the lower number because it may be due to a decrease in reporting.

Searle reviewed that in the past six months with approximately ——— , dispensed, there have been fewer than four reported medication errors and that this was a significant decrease since the launch of the product. Searle thinks that this decrease signals that the educational effort has been successful but the FDA did not fully concur with this conclusion. FDA expressed concern that the responses to 11, 12 and 32a of the survey highlighting that 10% of the doctors are still aware of confusion, suggests that this is an ongoing problem and requires continued correction.

Searle noted that they had changed the trade name prior to the approval of celecoxib at the request of the FDA to deal with the possibility of name confusion. At this time, they plan to ———

Searle expressed their concern that a

name change at this time would create a new set of problems and confusion and hopes it will not be necessary.

Dr. DeLap stated that it may not be possible to eliminate 100% of the errors but we must endeavor to pursue that goal. We must consider a better way to measure errors and a retrospective analysis may be one way. FDA (J. Phillips) offered to assist Searle and reiterated that the small number of medication errors that are reported may only be part of a much greater problem. Dr. DeLap emphasized that it is obvious that as long as the names are similar, Searle will have to continually educate the community to minimize name confusion. There is continuing concern that the errors are ongoing even at what may appear to be a low frequency.

FDA will continue to assess this issue internally and communicate with Searle all recommendations. It was suggested that Searle continue efforts to eliminate all medication errors and in addition evaluate possible new names in the event that all agree that a name change may be the best and/or only alternative.

Dr. Spivey noted that Searle had been approached by the media concerning the meeting FDA had with PhRMA trademark staff this morning (July 26, 2000) and noted the media has a continued interest in the results of the CorrectRx program. Mr. Phillips stated that the media does know that the data are under review but the FDA will not make any comment as to the review of the data. Dr. DeLap added that individual FDA reviewers would not make comments on the review of the data to the media and the FDA would only communicate with Searle.

CONCLUSION:

Searle will continue with all programs. Dr. DeLap advised Searle to be prepared with a new tradename in the event that alternative was necessary. Searle will consider means of better estimating the incidence of medication errors with Celebrex. FDA will continue discussion internally and communicate with Searle any further recommendations.

ACTION ITEM:

Minutes of meeting will issue within 30 days.

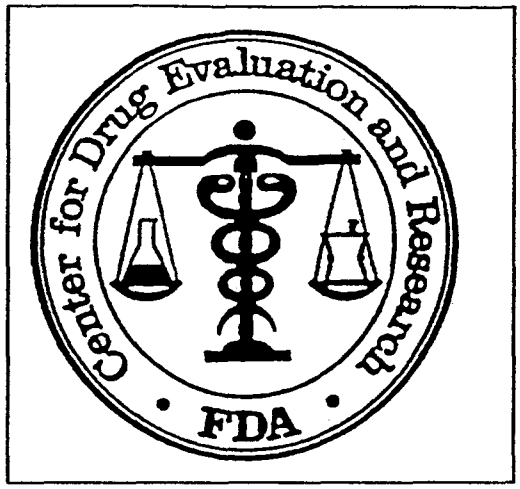
/S/ 8-28-00
Leslie Vaccari
Minutes Preparer

Concurrence: /S/ 28-00
Karen Midthun, M.D.
Division Director

Attachment: Overhead Copy-28 pages

Y. Kong – 550

FACSIMILE TRANSMISSION RECORD



From: Yoon Kong, Pharm.D.

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 10/5/00

To:

Name: Winifred M. Begley
Senior Director, Regulatory Affairs
Company: Searle
City: Skokie State: Illinois
Phone #: (847) 982-8155
FAX #: (847) 982-8090

Number of Pages (INCLUDING COVER PAGE): 1

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

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

Dear Winifred:

Please address the association between the UGI symptoms (nausea, vomiting, dyspepsea, abdominal pain) and the endoscopic ulcer results for each comparator in the endoscopic studies from the original Celebrex NDA submission. Please analysis of all subjects with UGI symptoms as well as only subjects who withdrew due to UGI symptoms.

Please give me a call if you have any questions or concerns.

Thank you

/S/ 10/5/00

Yoon Kong, Pharm.D.

CC: NDA 20-998
HFD-550/Div. Files
HFD-550/L. Goldkind / J. White / Y. Kong

CONFIRMATION

10/05/00 14:04

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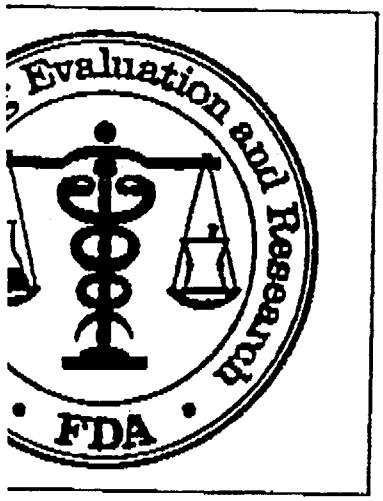

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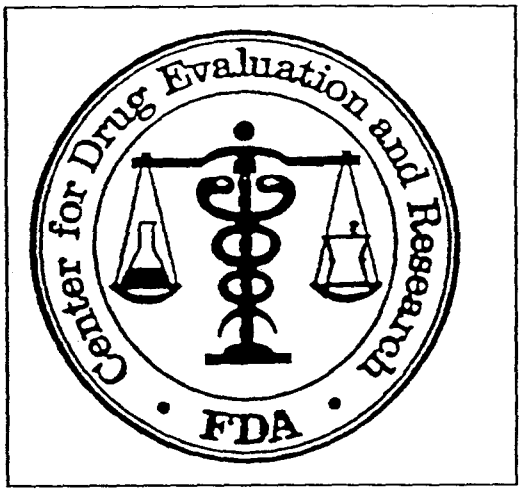

From: Yoon Kong, Pharm.D.

Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 10/11/00

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Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

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

Dear Winifred:

Our statistics reviewer would like some clarification on datasets submitted regarding CUSUGIE. The time to CUSUGIE was provided in the dataset, but not time to GI adverse events (AEs). To derive time to AEs, is this the difference between the date of AE and the date of the first dosing (e.g., is the time to moderate to severe GI AE calculated to be aedt2-sstart?)? Is this how time to CUSUGIE was calculated in datasets?

Please give me a call if you have any questions or concerns.

Thank you.

/S/ 10/11/00

Yoon Kong, Pharm.D.

cc: NDA 20-998/S-009
HFD-550/ Div. Files
HFD-725/ L. Lu/ Stan Lin

CONFIRMATION

10/11/00 06:53

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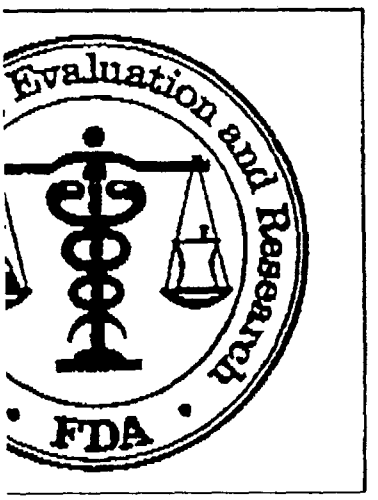

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Y Kong

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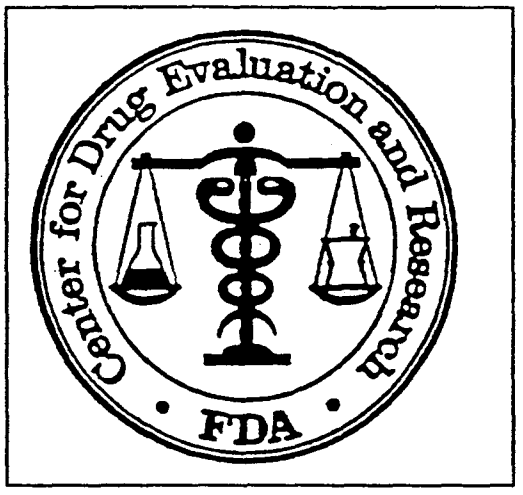

From: Yoon Kong, Pharm.D.

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 10/25/00

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FAX #: (847) 982-8090

Number of Pages (INCLUDING COVER PAGE): 1

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

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

Dear Winifred:

Please provide a list of the case numbers of patients who had CSUGIEs or CSUGIEs/GDU (both with and without an adverse event) for celecoxib, diclofenac, and ibuprofen in Table 2 (appendix 1.9, page 1981 of 24295 <N49-00-06-035_102).

Please give me a call if you have any questions or if you need clarification.

Thank you.

/S/ 10-25-00

Yoon Kong, Pharm.D.

faxed to person on 10-25-00

cc: NDA 20-998
HFD-550/Div. Files
/ J. White / L. Goldkind
/ Y. Kong

CONFIRMATION

10/25/00 08:49

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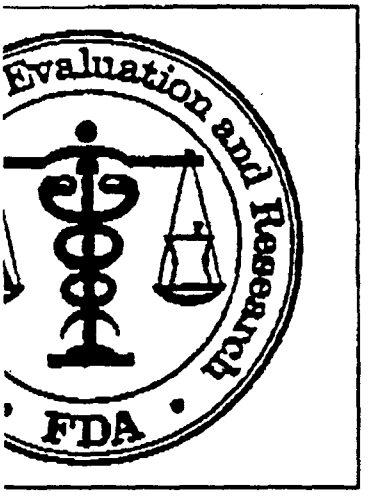

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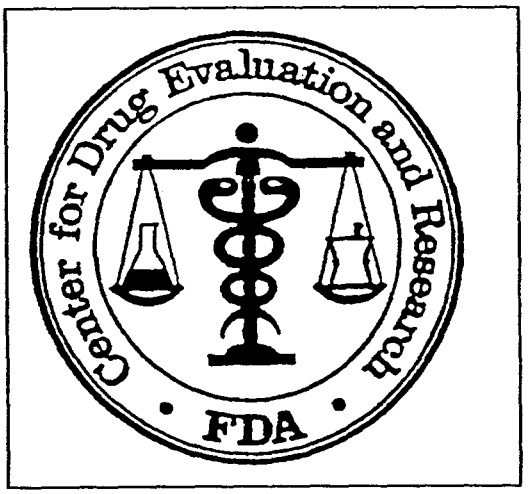

From: Yoon Kong, Pharm.D.

Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 11/16/00

To:

Name: Winifred M. Begley
Senior Director, Regulatory Affairs
Company: Searle
City: Skokie State: Illinois
Phone #: (847) 982-8155
FAX #: (847) 982-8090

Number of Pages (INCLUDING COVER PAGE): 6

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

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

Dear Winifred:

Please provide the following additional analyses for laboratory data as soon as this information can be made available to us since it directly impacts on the review progress of the application.

I. Additional Analyses for Laboratory Data

Please perform analyses on the whole of the study population and then on the subpopulations taking ASA and those not taking ASA (separated by treatment group of course). Anyone with these abnormalities at baseline should be excluded from the analysis, and these individuals should be listed separately along with their laboratory data. As an aid to the analyses that is requested by the reviewer, attached are the incomplete tables from his review; the blank boxes indicate where the numbers are to be filled in by the sponsor.

CONFIRMATION

11/16/00 12:22

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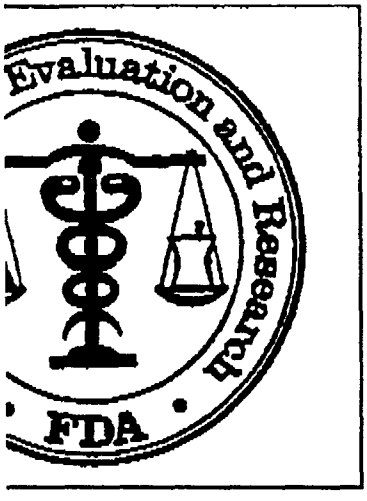

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Number of Pages (INCLUDING COVER PAGE): 6

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A. Table T45.1

1. Chloride <90 mmol/L and >120 mmol/L
2. Potassium <3.0 and 3.5 mmol/L and >5.0 and 5.5. mmol/L
3. Bicarbonate <20 mmol/L
4. Creatinine >132 and 176 mmol/L
5. Phosphate <0.64 and 0.96 and > 2.10 mmol/l
6. BUN >6.7 mmol/l
7. Creatinine >133 mmol/l

B. Table T48: Creatinine by BUN

1. Similar analysis using BUN > and ≤6.7 and Creatinine > and ≤133 mmol/l

2. For the analysis in the report, were these analyses segregated by the use of ASA? Please direct us to these analyses in the submission (if these analyeses were not performed previously, please do them).

C. Table T54

1. All of the Extreme High Criterion (page 563 of 24295) for maximum BP recorded at any time during trial rather than just at the end of the trial.

2. For the analysis in the report, have the changes in BP segregated by the use of ASA been analyzed? Please direct us to these analyses in the submission (if these analyeses were not performed previously, please do them).

II. Additional Analyses for SAEs

A. Table of Serious Adverse Events

1. Reviewer has grouped together some categories of SAEs, and was not able to calculate the incidence per person year. These appear in the tables (see below) as numbers without (x %); please fill in.

B. Reported Serious Renal and Cardiac Adverse Events

The next table summarizes the occurrence of selected serious adverse events relevant to renal and cardiac safety.

Serious Adverse Events (SAEs) Reported During Study[a].

Adverse Event	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Renal SAEs			
Hyper-, Hypo-kalemia[e]	0 (0%)	0 (0%)	0 (0%)
Acidosis[e]	0 (0%)	0 (0%)	0 (0%)
Nephrotic Syndrome[e]	0 (0%)	0 (0%)	0 (0%)
Edema[e]	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			
Arrhythmia 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]	16	2	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]	31	14	11
Myocardial Infarction	19 (0.8%)	4 (0.4%)	9 (0.8%)
Hypertension Aggravated	2 (<0.1%)	0 (0%)	0 (0%)
Thrombophlebitis Combined[d]	8	6	1

a. Data from electronic data submission, table T43. Incidence reported per 100 person-years.
b. Sum of atrial arrhythmia, atrial fibrillation, bradycardia and tachycardia.
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.

III. Changes in Laboratory Parameters (to be filled in by sponsor)

A. Extreme Changes from Baseline

The sponsor analyzed the lab data using a single set of cut-offs for 'extreme' values. Additional analyses were done at the request of this reviewer. Data is shown below for the maximum value recorded at any time during the trial. Similar results were seen if the final visit values were examined.

Extreme Laboratory Values from Entire Study Period[a].

Lab Test	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
BUN (mmol/l)			
>6.7[d]			
>14.3[d]	31/3692 (0.8%)	20/1849 (1.1%)	16/1786 (0.9%)
Creatinine (mmol/l)			
>133[c]			
>265.2	1/3692 (<0.1%)	0/1850 (0%)	0/1786 (0%)
Potassium (meq/l)			
<3.5			
<3.0			
>5.0			
>6.0	11/3673 (0.3%)	3/1837 (0.2%)	0/1770 (0%)[b]
Chloride (mmol/l)			
<75	0/3690 (0%)	0/1847 (0%)	0/1786 (0%)
<90			
>110			
>120			
Bicarbonate (mmol/l)			
<20			
<15	1/3689 (<0.1%)	2/1844 (0.1%)	0/1782 (0%)
>35	13/3689 (0.4%)	7/1844 (0.4%)	1/1782 (0.2%)
Phosphate (mmol/l)			
<0.32	0/3676 (0%)	0/1841 (0%)	0/1771 (0%)
<0.64			
<0.96			
>2.10			
>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 Value = 0.021 per sponsor.
c. Corresponds 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.

These analyses were done separately for the patients taking ASA along with the NSAID and those not taking ASA. For the most part, these results mirrored the combined analysis. One exception was the incidence of extreme hyperkalemia, which was more common in the celecoxib group relative to the comparators. The table below shows the data for increases in BUN/Crt, K^+ and HCO_3^- grouped according to the use of ASA.

Extreme Laboratory Values from Entire Study Period By ASA Use[a].

Lab Test	Celecoxib 400 mg BID		Diclofenac 75 mg BID		Ibuprofen 800 mg TID	
	ASA	No ASA	ASA	No ASA	ASA	No ASA
BUN (mmol/l)						
>6.7[d]						
>14.3[d]	12/829 (1.4%)	0/2863 (0%)	9/421 (2.1%)	0/1428 (0%)	5/386 (1.3%)	0/1400 (0%)
Creatinine (mmol/l)						
>133[c]						
>265.2	1/829 (0.1%)	19/2864 (0.7%)	0/422 (0%)	11/1428 (0.8%)	0/386 (0%)	11/1400 (0.8%)
Potassium (meq/l)						
<3.5						
<3.0						
>5.0						
>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						
<90						
>110						
>120						
Bicarbonate (mmol/l)						
<20						
<15						
>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						
<0.64						
<0.96						
>2.10						
>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 during trial relative to baseline.
c. Corresponds 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.

Because of the important interaction between changes in BUN and serum creatinine (SCrt) the incidence of combined abnormalities of these two lab measurements was examined.

Incidence of Combined Abnormalities in BUN and Scrt[a, b].

Parameter	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
BUN ≥14.3 mmol/l and SCrt ≥159 mmol/l[c]	14/3702 (0.38%)	6/1852 (0.34%)	7/1807 (0.39%)
BUN > 6.7 and SCrt > 133 mmol/l[d]			

a. Data from electronic datasets table T48 and at request of reviewer from sponsor.
b. SCrt = serum creatinine.
c. Corresponds to a BUN/Crt of 40/3.0 mg/dl.
d. Corresponds to a BUN/Crt of 20/1.5 mg/dl.

These same data, grouped according to ASA use, appear below.

Incidence of Combined Abnormalities in BUN and Scrt Grouped by ASA Use[a, b].

Parameter	Celecoxib 400 mg BID		Diclofenac 75 mg BID		Ibuprofen 800 mg TID	
	ASA	NoASA	ASA	NoASA	ASA	NoASA
BUN ≥14.3 mmol/l and SCrt ≥159 mmol/l[c]						
BUN > 6.7 and SCrt > 133 mmol/l[d]						

a. Data at request of reviewer from sponsor.
b. SCrt = serum creatinine.
c. Corresponds to a BUN/Crt of 40/3.0 mg/dl.
d. Corresponds to a BUN/Crt of 20/1.5 mg/dl.

B. Changes in Blood Pressure

While there were no laboratory measurements related to cardiac function performed routinely, the sponsor did analyze the changes in blood pressure (BP) recorded for those subjects with both baseline and at least one follow-up BP reading. The changes in the mean BP for the three treatment groups hovered around 0 for the trial and were of little clinical significance. The incidence of abnormal elevations in BP is summarized below.

Incidence of BP Elevations During Study[a].

Parameter	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Sitting Systolic BP ≥15% increase over baseline at final visit	315/2925 (10.8%)	163/1434 (11.4%)	173/1387 (12.5%)
Sitting Systolic BP ≥15% increase over baseline at any time			
Sitting Diastolic BP ≥15% increase over baseline at final visit	298/2925 (10.2%)	146/1434 (10.2%)	134/1387 (9.7%)
Sitting Diastolic BP ≥15% increase over baseline at any time			

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

***Were these results similar to those found when analyses were done according to whether the patient was also taking ASA (data not shown)?

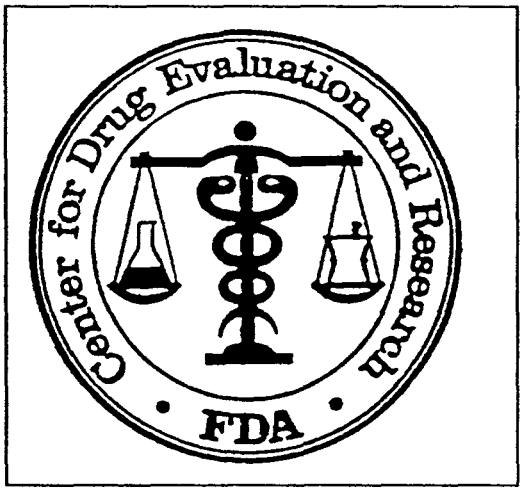
Please give me a call if you have any questions or need clarification at (301) 827-2090.

Thank you.

/S/

Yoon Kong, Pharm.D.

FACSIMILE TRANSMISSION
RECORD



From: Yoon Kong, Pharm.D.

Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 11/17/00

To: Name: Winifred M. Begley
Senior Director, Regulatory Affairs
Company: Searle
City: Skokie State: Illinois
Phone #: (847) 982-8155
FAX #: (847) 982-8090
Number of Pages (INCLUDING COVER PAGE): 2

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

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

Dear Winifred:

Please provide the following information with respect to the attached table:

1. Confirm accuracy of the attached table.
2. Create a similar table for mortality and cardiovascular mortality based on the use of ASA by the patients.
3. Consider whether a time-to-event analysis for the deaths, similar to what was done with the original celecoxib NDA, would be of interest.

If you have any questions or need clarification, please contact me at (301) 827-2090.

Thank you.

/S/

Yoon Kong, Pharm.D.

Mortality Rates from Celecoxib Trial[a]

	Celecoxib	Diclofenac	Ibuprofen
Deaths/ Person Years	13/2340 (0.56%)	8/1080 (0.74%)	7/1122 (0.62%)
Cardiac Deaths/ Person Years[b]	6/2340 (0.26%)	4/1080 (0.37%)	4/1122 (0.36%)

a. Data from electronic data submission, appendix 2.9.1 and page 174 of 24295.
b. Deaths ascribed to ischemic cardiac causes (excluding 2 cases of CHF).

MESSAGE CONFIRMATION

11/17/00 15:26

J.	MODE	BOX	GROUP
77	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
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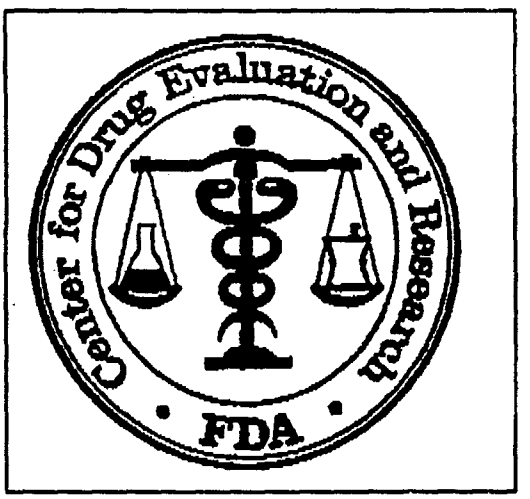
FACSIMILE TRANSMISSION RECORD



From: Yoon Kong, Pharm.D.

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 11/17/00

To:

Name: Winifred M. Begley
Senior Director, Regulatory Affairs
Company: Searle
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Phone #: (847) 982-8155
FAX #: (847) 982-8090
Number of Pages (INCLUDING COVER PAGE): 2

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

Re: NDA 20-998/S-000

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Winifred M. Begley	**From:** Yoon Kong, Pharm. D.
Fax: (847) ~~982-8155~~ 982-8090	**Fax:** 301-827-2531
Phone: (847) ~~982-8090~~ 982-8155	**Phone:** 301-827-2090
Pages: 1 (including cover page)	**Date:** November 29, 2000
Re: NDA 20-998/S-009	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

● Comments:

Please provide the following information regarding Study N 499-99-02-123:

1. Please provide the dissolution results from the acid stage in order to demonstrate that the diclofenac sodium tablets used in a safety trial remain intact in the stomach following oral administration. Also, please provide any other supportive evidence, if available.
2. SAS codes and data set for testing bioequivalence (study Protocol N49-99-02-123).
3. Stcks plots for AUC, Cmax, Tmax (comparing the 2 formulations).

Please do not hesitate to call me if you have any further questions or need clarification.

Thank you.

Yoon Kong, Pharm.D.

/s/

Yoon Kong
11/30/00 07:51:11 AM
CSO

Yoon Kong
11/30/00 07:52:48 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Winifred M. Begley	**From:** Yoon Kong, Pharm. D.
Fax: (847) 982-8090	**Fax:** 301-827-2531
Phone: (847) 982-8155	**Phone:** 301-827-2090
Pages: 2 (including cover page)	**Date:** December 6, 2000
Re: NDA 20-998/S-009	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

● Comments:

Dear Winifred,

Please find attached information request from Dr. Throckmorton regarding performing additional analyses.

Please do not hesitate to call me if you have any further questions or need clarification.

Thank you.

/S/ 12-6-00 faxed to sponsor on 12-6-00

Yoon Kong, Pharm.D.

1. In a paper Searle sent me earlier (Peter East I believe sent it to me) on the incidence of renal injury in an outpatient setting for patients taking Ibuprofen (Murray et al, Am J Med Sci, 299: 222-229, 1990), they used the following analysis (analyze BUN and SCrt separately):

    a. Normal defined as Baseline BUN ≤18 mg/cl (6.4 mmol/l) and SCrt /2 (110).
    b. Abnormal otherwise

    Renal impairment counted as the following lab values:

    'Renal impairment' for patients normal at baseline
    a. For BUN, any increase ≥20 mg/dl
    b. For SCrt, any increase to ≥1.2

    'Renal impairment' for patients abnormal at baseline
    a. For BUN, any increase ≥40 mg/dl
    b. For SCrt, any increase of twofold to <2.0 or any final value greater than 2.5

    'Serious renal impairment' for patients normal at baseline
    a. For BUN, any increase ≥10% over baseline
    b. For SCrt, any increase ≥10% over baseline

    'Serious renal impairment' for patients abnormal at baseline
    a. For BUN, any increase 2-fold over baseline
    b. For SCrt, any increase of twofold over baseline

2. One standard definition of renal failure (from Manual of Clinical Problems in Nephrology) is as follows: Rise in SCrt of ≥0.5 mg/dl if the baseline value is ≤3.0 mg/dl, or at least 1.0 mg/dl if the baseline level is >3.0 mg/dl.

What I'm trying to do is get a handle on whether the event rates in the trial were where we would expect them to be, by comparing the rates seen with rates from other databases. To date, the paper I cited above is the only good database I know of (you may know others), hence that analysis. If you have other lab definitions of renal injury I'd love to see them applied to this dataset as well.

********** -COMM. JOURNAL- ********** DATE DEC-06-2000 ***** TIME 09:42 *** P.01

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-FDA CDER ODEV DAAO HFD550-

********** - ***** - 301 827 2531- **********

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Winifred M. Begley	**From:** Yoon Kong, Pharm. D.
Fax: (847) 982-8090	**Fax:** 301-827-2531
Phone: (847) 982-8155	**Phone:** 301-827-2090
Pages: 2 (including cover page)	**Date:** December 6, 2000
Re: NDA 20-998/S-009	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

● Comments:

Dear Winifred,

Please find attached information request from Dr. Throckmorton regarding performing additional analyses.

Please do not hesitate to call me if you have any further questions or need clarification.

Thank you.

/S/ 6-06

Yoon Kong, Pharm.D.

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Winifred M. Begley	**From:** Yoon Kong, Pharm. D.
Fax: (847) 982-8090	**Fax:** 301-827-2531
Phone: (847) 982-8155	**Phone:** 301-827-2090
Pages: 1 (including cover page)	**Date:** December 6, 2000
Re: NDA 20-998/S-009	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

● Comments:

Dear Winifred,

Per my voicemail message this morning; please provide the following clinical information requests.

1) Please clarify if there is any original documentation available that supports the narratives of Appendix 2.15.

2) Also, please separate out the OTCs in Appendix 2.14. Please comment on why any of these NSAIDS (other than the study medications and ASA used for prophylaxis) were allowed during the trial, since the protocols specifically excluded either prescriptions or OTC NSAIDs.

Please do not hesitate to call me if you have any further questions or need clarification.

Thank you.

/S/ 12-6-00 faxed to sponsor on 12-6-00

Yoon Kong, Pharm.D.

********** -COMM. JOURNAL- ********** DATE DEC-06-2000 ***** TIME 08:09 *** P.01

MODE = MEMORY TRANSMISSION START=DEC-06 08:08 END=DEC-06 08:09

FILE NO.= 060

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-FDA CDER ODEV DAAD HFD550-

********** - - ***** - 301 827 2531- **********

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Winifred M. Begley	**From:** Yoon Kong, Pharm. D.
Fax: (847) 982-8090	**Fax:** 301-827-2531
Phone: (847) 982-8155	**Phone:** 301-827-2090
Pages: 1 (including cover page)	**Date:** December 6, 2000
Re: NDA 20-998/S-009	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

● Comments:

Dear Winifred,

Per my voicemail message this morning; please provide the following clinical information requests.

1). Please clarify if there is any original documentation available that supports the narratives of Appendix 2.15.

2) Also, please separate out the OTCs in Appendix 2.14. Please comment on why any of these NSAIDS (other than the study medications and ASA used for prophylaxis) were allowed during the trial, since the protocols specifically excluded either prescriptions or OTC NSAIDs.

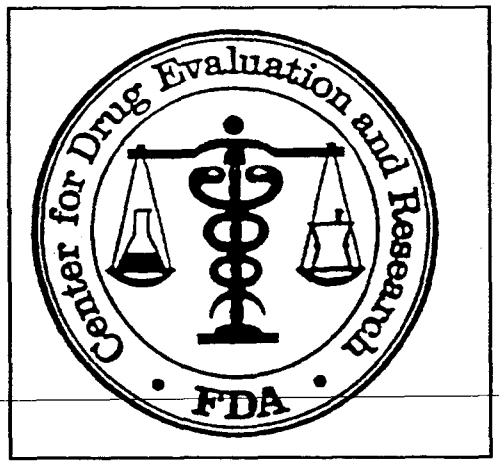
Please do not hesitate to call me if you have any further questions or need clarification.

Thank you.

/S/ 12-6-00

Yoon Kong, Pharm.D.

FACSIMILE TRANSMISSION
RECORD



From: Yoon Kong, Pharm.D.

Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 12/11/00

To:

Name: Winifred M. Begley
Senior Director, Regulatory Affairs
Company: Searle
City: Skokie State: Illinois
Phone #: (847) 982-8155
FAX #: (847) 982-8090

Number of Pages (INCLUDING COVER PAGE): 2

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

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

Dear Winifred:

Please provide the following information concerning narratives for AEs as soon as it can be made available for our review.

In order to expedite the drug safety review for this product the following file is requested.

Please provide a special review aid as a single file with narratives for ALL adverse events. The specifications are:

1) It must be a **text file** (e.g., narratives.txt).
2) This single file should contain all narratives across all studies.
3) Keep the narrative as a single paragraph—length of paragraph does not matter.
4) The first column of the narrative should begin with the **UNIQUE patient identifier** variable, which must have the same name and format as used in all other data sets. This variable is used to link

the narratives to the data provided for the entire NDA. See examples below:

Example 1:

2456_211_02114567[tab]. Then begin your description of the adverse event, which should include the significant information about the event…

3056_201_02015789. This is a 32-year-old white female who presented with acute pancreatitis and after 7 days developed an infection of the right leg. She was treated with Cipro 500 mg IV T.I.D. x 10 days. She developed renal failure as evidenced by… Her lab values returned to normal after 12 days and she returned to normal and functional state of well being.

If you have any questions or need clarification, please let me know.

Thank you.

/S/

Yoon Kong, Pharm.D.

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Winifred M. Begley	**From:** Yoon Kong, Pharm. D.
Fax: (847) 982-8090	**Fax:** 301-827-2531
Phone: (847) 982-8155	**Phone:** 301-827-2090
Pages: 1 (including cover page)	**Date:** December 13, 2000
Re: NDA 20-998/S-009	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

● Comments:

Dear Winifred,

Please provide the following additional data requested:

A dataset for ITT patients including patient ID, treatment group, time to combined CSUGIE/GDU events, censoring status of time to combined CSUGIE/GDU events (0 (zero) for censoring and 1 (one) for event), time to withdrawal due to lack of arthritis efficacy.

Please let me know if you have any questions or need clarification.

Thank you.

/S/

Yoon Kong, Pharm.D.