

PHARMACIA

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

March 21, 2002

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

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

Dear Dr. Simon:

In response to your request of March 11, 2002, we now provide event rates for individual and grouped CV events using Kaplan-Meier (KM) rates and exposure-adjusted rates-incidence rates have been previously submitted. Please see attached tables and figures. All three presentations of the data support the conclusion that there is no increase in CV adverse events associated with celecoxib relative to the conventional NSAIDs, diclofenac and ibuprofen.

In considering the relative merits and issues of these three alternative presentations of the data in the label, we propose that the use of incidence rates, as previously agreed with the Division, is the clearest presentation of the CV safety data for celecoxib and will be most readily understood by the practitioner for the following reasons:

1. The use of incidence rates for CV adverse events in the celecoxib label is consistent with the display of other adverse event information in the celecoxib label. The use of incidence rates therefore allows physicians to understand most readily the safety of a celecoxib in an integrated manner.
2. The use of KM (or exposure-adjusted) rates for CV adverse events combined with the use of incidence rates for other adverse events may lead practitioners to overestimate the occurrence of CV adverse events in patients on celecoxib relative to other adverse events in the label for celecoxib. Physicians may thus derive an inaccurate view of the overall safety of celecoxib.
3. KM rates suffer from the phenomenon of "tail instability" which can lead to imprecise estimates of event rates once the number of patients at risk diminishes (a potential issue in CLASS).
4. Exposure-adjusted rates imply a constant event rate over time, an assumption that may not be true for CV adverse events for all COX-2 inhibitors.

**APPEARS THIS WAY
ON ORIGINAL**

March 12, 2002

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

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

Dear Dr. Simon:

As a follow-up to our March 8, 2002 meeting regarding CLASS labeling, additional analyses were performed to determine the incidence of clinically significant decreases in hemoglobin (>2g/dl decrease from baseline), confirmed by repeat testing. These incidence rates and the results of comparisons between celecoxib and the NSAID comparators for the cohort of all patients are summarized in Table 1. The comparisons were performed with Fisher's Exact test. Also included in Table 1, for completeness, are the results for the incidence of >2 g/dl hemoglobin reductions from baseline in one or more occasions. The same analyses were performed for non-ASA users and ASA users, and the results are summarized in Tables 2 and 3, respectively. The two-sided 95% confidence intervals for the incidence of >2g/dl hemoglobin reductions are presented in Table 4 for the cohort of all patients. The confidence intervals were based on Clopper-Pearson method.

Results in Tables 1-3 demonstrate consistent risk ratios between an NSAID comparator and celecoxib in hemoglobin decreases, whether with single- or repeated- value criterion, or in the cohort of all patients, ASA users, or non-ASA users. Given the highly significant and robust findings in the analysis of incidence of repeated >2g /dl hemoglobin decreases (.002 vs. diclofenac, < .001 vs. ibuprofen), significance would be preserved even with a conservative p-value adjustment such as Bonferroni.

The definition of clinically meaningful changes in hemoglobin or hematocrit was pre-specified and the analyses were pre-defined in the statistical analysis plan. As shown in the CLASS report, there is a lower incidence of reductions in hemoglobin/hematocrit comparing celecoxib to the NSAID comparators, diclofenac and ibuprofen. These results are consistent with those shown in Tables 1-3 in this submission. The results are robust in that:

1. They are corroborated by an analysis from CLASS of changes in hemoglobin/hematocrit that are confirmed upon repeat testing.

2. They are supported by a similar analysis of the NDA database comparing celecoxib to NSAIDs combined as well as placebo.
3. Treatment differences are similar between celecoxib and all tested NSAID comparators (ibuprofen, diclofenac, and naproxen) across databases examined.

The differential effects seen between celecoxib and the NSAID comparators has a mechanistic basis related to the lack of platelet effects associated with specific COX-2 inhibition. One clinical outcome of such pharmacological selectivity with celecoxib could be expected to manifest as reductions in hemoglobin and/or hematocrit. Consistent with this mechanism-related hypothesis, the results of analyses of clinically significant hemoglobin/hematocrit decreases showed a robust, significant risk reduction over NSAID comparators.

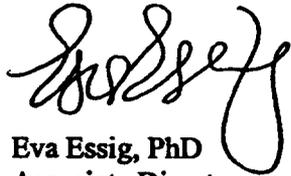
Importantly, the magnitude of changes indicate that the observed treatment differences are medically important. First, a reduction of hemoglobin of 2 g/dl is equivalent to a decrease in 2 units of packed red cells. Secondly, patients experiencing such decreases exhibited a higher incidence of cardiovascular events (thromboembolic events, CHF, syncope) than those without such decreases. The risk of having serious cardiovascular adverse events in patients with hemoglobin/hematocrit decreases of 2 g/dl and/or 10%, respectively was 3.1 times higher than in patients without such decreases. The observed treatment differences thus are medically meaningful in that a reduced incidence of such decreases would be relevant to the care of arthritis patients who would be susceptible to the consequences of a decrease in blood oxygen carrying capacity (e.g. arthritis patients with atherosclerotic cardiovascular disease or CHF).

The observations described above offer strong rationale for a quantitative description of the treatment-related differences seen with regard to hemoglobin changes so that prescribers are provided sufficient context to evaluate the findings and the implications for their patients. While we continue to maintain that p values are the most appropriate means to describe the data, in the interest of bringing these labeling negotiations to a close and based on the reasoning presented above, it is appropriate to retain the wording "... significantly fewer..." in the current labeling proposal together with use of confidence intervals as an alternative to p values. Our labeling proposal is as follows:

Attached please also find a revised marked up version of the label dated March 12, 2002.

We look forward to our next discussion and bringing this labeling supplement to a close.

Sincerely,

A handwritten signature in black ink, appearing to read 'Eva Essig', written in a cursive style.

Eva Essig, PhD
Associate Director
Global Regulatory Affairs
847.982.8980
847.982.8090 (fax)

EE/nb

**APPEARS THIS WAY
ON ORIGINAL**

February 11, 2002

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

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

Dear Dr. Simon:

Please find attached a revised Celebrex label (Attachment 1).

In brief, we have made the following modifications:

General:

- The long-term outcome study is referred to as "CLASS" throughout the label.
- We have substantially reduced the number of places the CELEBREX 400 mg BID dose is identified as "(4x and 2x the approved OA and RA doses, respectively and the approved dose for FAP)". It now only appears in the "Use with Aspirin" where CLASS is first described and in "Adverse Reactions" in conjunction with Tables 7 and 8.

Clinical Studies:

- The "Endoscopic Studies" section has been substantially shortened. The aspirin data derived from endoscopic studies (previously under "Use with Aspirin") has been moved to this subsection to reside with the other endoscopic data.
- The "Use with Aspirin" section has been expanded to include a more detailed description of the CLASS study and results of the primary study endpoint.

Warnings:

- The complicated and symptomatic ulcer rates for Celebrex have been incorporated into Table 5.
- Advanced Renal Disease has been revised as agreed upon

Precautions:

- Pursuant to your request, minor changes to certain sections have been made.

Adverse Reactions:

- Table 7 has been modified to remove p values around individual events.

- Table 8 has been modified to only include important cardiovascular events in particular those indicative of thromboembolic events.
- As requested, attached is a table reflecting serious adverse events expressed as cumulative rates (Attachment 2). However, since crude rates are currently included in other parts of the label and common to/consistent with other labels, we do not endorse expression of event rates in any form other than crude rates.
- The subsection relating to adverse events from the analgesia and dysmenorrhea studies has been reduced. A decision has been made not to remove the whole subsection as other indication-specific subsections are present and communication of similarities in ADR profile between arthritis and pain populations is meaningful to the practitioner.

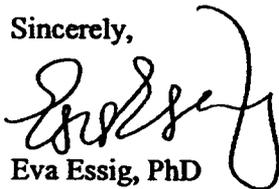
Overdosage:

- We have maintained the description of symptoms following overdose.

At the meeting, we would like to gain concurrence on the above changes in the revised label. Additionally, we intend to engage in further discussion regarding the requested inclusion of post-marketing renal events in the label as well as the presentation and analysis of the hematologic data.

We look forward to our discussions on February 13. Attendees at the meeting will be from Pharmacia: Dr. P. Needleman, Dr. T. Koestler, Mr. N. Wolf, Dr. R. Spivey, Dr. R. Garutti, Dr. S. Geis, Dr. J. Lefkowitz, Dr. V. Shu, and Dr. E. Essig, and from Pfizer: Dr. M. Fletcher and Mr. S. Cristo.

Sincerely,



Eva Essig, PhD
Associate Director
Global Regulatory Affairs
847.982.8980
847.982.8090 (fax)

EE/nb

**APPEARS THIS WAY
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NDA SUPPL AMENDMENT
SEB-009/B

PHARMACIA

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

February 4, 2002

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

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FEB 06 2002
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NDA 20-998 S/009
Celebrex® (Celecoxib)

Dear Dr. Simon,

Please refer to our submission of December 20, 2001 in which we provided our revised proposal for Celebrex labeling changes. Kindly also refer to a discussion on February 1, 2002 between Dr. R. Garutti of Pharmacia and Dr. L. Goldkind.

In the above proposal, we included the FDA proposed language modification to the "Advanced Renal Disease" subsection of "Warnings". Upon further review of the safety database and consistent with assessments made by Dr. Throckmorton in his review of CLASS entitled "Comparative Review of the Safety of Celebrex, Diclofenac and Ibuprofen" (dated 1.05.01), there are no suggestions that the renal effects of Celebrex are any different from those of other NSAIDs. For this reason, we maintain that the current template NSAID labeling should remain. This is also consistent with the review provided by OPDRA in the documentation made available for the Advisory Committee convened for consideration of CLASS study results.

The current labeling clearly states that there is no information regarding use of Celebrex in patients with advanced kidney disease, which was appropriate at the time of the NDA approval.

Statements referencing acute renal failure and use in patients with impaired renal function are already contained in the current "Adverse Reactions" and "Precautions- Renal Effects" sections of the label, respectively. Monitoring instructions are clearly stated in the currently approved template labeling. Again, these should be no different from other NSAIDs.

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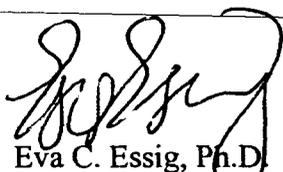
Therefore our proposed label is as follows:

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of CELEBREX in patients with advanced kidney disease. Therefore, treatment with CELEBREX is not recommended in these patients. If CELEBREX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS - Renal Effects).

We would appreciate your consideration of this revised text.

Sincerely,



Eva C. Essig, Ph.D.
Associate Director
Regulatory Affairs
Direct Line 847.982.8980
Fax 847.982.8090

**APPEARS THIS WAY
ON ORIGINAL**

December 20, 2001

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

COMPLETE RESPONSE TO JUNE 12, 2001 ACTION LETTER

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

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

Dear Dr Lee,

Please refer to our labeling supplemental (S-009) for New Drug Application 20-998 and the Agency's second approvable letter dated June 12, 2001. Please also refer to Dr. Woodcock's response of December 7, 2001 to the Formal Dispute Resolution Request submitted by Pharmacia on September 26, 2001.

We now provide a complete response that addresses the Agency's proposed labeling identified in your letters of June 12, 2001 and December 7, 2001. Please note that a safety update to the NDA incorporating safety data through June 30, 2001 was submitted to the NDA/S-009 on November 26, 2001.

Attached are two documents. The first shows a side-by-side comparison of the FDA proposed labeling of June 12 on the left-hand column and the Pharmacia proposal on the right-hand column. The second document is a Word version of the currently approved Celebrex® Package Insert (dated October, 2001) with mark-up edits of the Pharmacia proposed changes. This full text label is also provided on disk.

We agree with Dr. Woodcock that the important safety information for Celebrex®, derived from the study, should be included in the Celebrex® Package Insert. We have modified the following sections to incorporate these important data:

- Clinical Pharmacology: Renal Insufficiency, Use with Aspirin, Platelets
- Warnings: Gastrointestinal, Advanced Renal Disease
- Precautions: Hematological Effects, Laboratory Tests, Drug Interactions- Aspirin, Geriatric Use
- Adverse Reactions
- Overdosage

In particular, these modifications to the "Use with Aspirin" and "Warnings" sections appropriately address the safety of Celebrex[®] in patients at high risk for GI events. In compliance with the draft labeling Guidance, the comparative safety data is clearly represented and appropriately placed in the "Adverse Reactions" section.

Should you have any questions, please contact the undersigned.

Sincerely,


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

Fax (847) 982-8090

Attachment

EE/jr

**APPEARS THIS WAY
ON ORIGINAL**

SE8-009/54

PARVIA

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

ember 26, 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

RECEIVED
NOV 27 2001
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NDA 20-998 S/009
Celebrex® (celecoxib)

Dear Dr. Bull,

In accordance with 21 CFR 314.50(d)(5)(vi)(b) we hereby submit the 120-day safety
te report for NDA 20-998 Celebrex®. This report summarizes the safety
information obtained after submission of this supplement (June 12, 2000) for patients
involved in 17 studies through June 30, 2001 and from postmarketing experience through
December 31, 2000.

Should you have any questions about this submission, please do not hesitate to contact
the undersigned.

Sincerely,

Barbara Johnson for

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

*VJK
11/30/01
WITTON*

Attachments

cc:

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

November 12, 2001

Ms. Kim Colangelo,
Office of Review Management (HFD-002)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike, Room 6027
Rockville, MD 20852

RECEIVED

NOV 13 2001

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SE8-009/NC

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

Dear Ms. Colangelo,

As per your request to Dr. Spivey, please find attached the collection of slides presented at our meeting with Dr. Woodcock on November 7, 2001.

Pharmacia participants were the following:

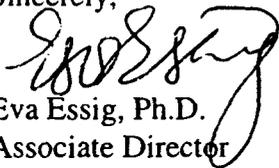
- Eva Essig, PhD, Associate Director, Global Regulatory Affairs
- Steve Geis, MD, PhD, Group Vice President, Clinical Research
- Jim Lefkowitz, MD, Senior Director, Clinical Research
- Philip Needleman, PhD, Executive Senior V.P., Chief Scientific Officer, Chairman R&D
- Richard Spivey, PhD, Senior Vice President, Corporate Technical Policy
- Neil Wolf, Group Vice President, Global Prescription Business

Pfizer participants were the following:

- Holly Crosbie-Foote, Worldwide Leader, Celebrex Marketing
- Mark Fletcher, MD, Global Clinical Leader, Clinical Research

Should you have any questions, please contact the undersigned.

Sincerely,



Eva Essig, Ph.D.
Associate Director
Global Regulatory Affairs
(847) 982-8980
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Not
12/3/01
written

cc: J. Bull
Attachment: Slide Presentation

EE/jr

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October 15, 2001

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

Dr. Bull, M.D., Director
Division of Anti-inflammatory, Analgesic
and Ophthalmologic Drug Products
Office of Drug Evaluation V
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1201 Corporate Boulevard
Rockville, MD 20850

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OCT 17 2001
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NDA 20-998 S/009
Celebrex® (celecoxib)

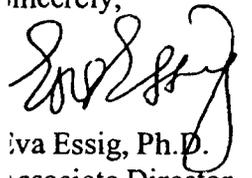
Dear Dr. Bull,

Please refer to your information request of September 21, 2001, pursuant to the August 10, 2001 meeting with Dr. Kweder.

In response to an identified list of analyses for the hematocrit and hemoglobin data, we provide the attached summary document and appendix.

If you have any questions about this submission, please do not hesitate to contact me. I am personally signed.

Sincerely,



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

Note
10/17/01
WITTON

Attachments

DE/jr

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SE8-009/NC

PHARMACIA

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

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September 26, 2001

Formal Dispute Resolution Project Manager (DRPM)
Food and Drug Administration
Center for Drug Evaluation and Research
Mail Code HFD-002
5600 Fishers Lane,
Rockville, MD 20857

RECEIVED
SEP 27 2001
MEGA/CDER

Re: **FORMAL DISPUTE RESOLUTION REQUEST**
Celebrex (celecoxib)
NDA # 20-998/S-009

- Division/Office where application is filed and which issued original decision: Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
- Last agency official who attempted to formally resolve the matter: Dr. S. Kweder, Acting Director, Office of Review Management
- Name, title and telephone and fax numbers of company contact: Dr. Richard Spivey, Senior Vice President, Global Regulatory Affairs; Phone no. (908) 901-8837; Fax no. (908) 901-1924.

Dear Sir/Madam:

Pursuant to FDA Guidance for Industry entitled "Formal Dispute Resolution: Appeals above the Division Level" (dated February 2000), we are requesting formal dispute resolution in relation to the aforementioned Celebrex CLASS Supplemental New Drug Application (SNDA). Attached to this letter is a briefing document (Attachment 1) from Pharmacia Corporation ("Pharmacia") relative to the SNDA which outlines the issues between the Division of Anti-Inflammatory, Analgesics and Ophthalmologic Drug Products ("Division") and Pharmacia. In an attempt to resolve the stated differences, we are requesting the opportunity to meet with Dr. J. Woodcock and also ask that Dr. Robert Temple be present at the meeting.

G.D. Searle & Co, now G. D. Searle LLC, a wholly-owned subsidiary of Pharmacia, submitted its supplemental New Drug Application dated June 12, 2000 pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for CELEBREX (celecoxib capsules), seeking changes to the Warnings and Clinical Studies sections of the labeling based on a large, randomized, double-blind study evaluating the long-term gastrointestinal effects of CELEBREX compared with two other non-steroidal anti-

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inflammatory drugs. The CLASS outcomes study was one of the largest studies ever conducted in arthritis, involving 386 sites (US/CANADA) with 7968 patients. Indeed, FDA officials during the Advisory Committee hearing noted that a database like the CLASS database does not come along very often. (February 7, 2001, Transcript, p 211, Dr. DeLap). Specifically, the Company believes that the labeling for CELEBREX should properly include comparative data (relative to CELEBREX, diclofenac and ibuprofen) on the incidence of symptomatic ulcer and ulcer complications ("combined endpoint") for the entire patient cohort and for the non-aspirin (ASA) cohort with applicable confidence intervals and p-values. The company also seeks inclusion of protocol pre-specified hematocrit and hemoglobin data in the labeling.

The data that Pharmacia seeks to include in the labeling further delineates the safety profile of CELEBREX and will help to ensure that health care practitioners are provided with complete and accurate information so they can make an informed decision with regard to the use of CELEBREX. Pharmacia believes the failure to allow this data in the approved labeling does a public disservice to prescribers and patients alike and is inconsistent with FDA's historical record for: 1) labeling changes for important safety information derived from lesser evidence standards than a controlled clinical trial; and 2) labeling changes based on prospectively collected clinical study data, even though the endpoint was not prespecified for analysis in an integrated statistical plan.

The document that is included in this package provides the continued statistical and clinical support for Pharmacia's request that certain safety information be included in the labeling.¹ This present letter provides the policy context in which Pharmacia believes its labeling request should be considered and decided.

I. SUMMARY OF PHARMACIA'S POSITIONS

Pharmacia has acknowledged in all interactions with the Division that the CLASS study failed to meet its primary endpoint. However, as set forth more fully in the attached document, the analysis of a key endpoint, such as combined complicated and symptomatic ulcers, has statistical validity, especially given that both components were prespecified. This is true because the data would not have been collected in any different manner, nor would the analysis have been done any differently, had the combined endpoint been pre-specified.

Pharmacia has identified and examined four key issues in its attached documentation with regard to its meeting request:

- The FDA proposed labeling does not address the issue that the primary outcome of the CLASS study (complicated ulcers) is subject to bias by informative censoring that renders the pre-specified analysis of the primary outcome invalid. Sole presentation of the primary outcome for CLASS in the label would therefore provide misleading

¹ The Division and the Company have exchanged numerous versions of the appropriate language to be included in the final approved labeling for CELEBREX to reflect the clinical study results from CLASS, and those are provided as a 4-column table in Attachment 2.

information to clinicians. The combined endpoint of complicated and symptomatic ulcers (which is based on determinations of complicated and symptomatic ulcer rates that were prespecified and determined in a blinded fashion) is both clinically appropriate and less biased. Furthermore, the FDA proposed labeling does not reflect prior discussion with the agency on these points and is inconsistent with the draft Guidance for Industry on Clinical Studies Sections of the label.

- Omission of the combined endpoint in the FDA proposed labeling ignores medically meaningful information, is inconsistent with the NSAID template labeling and precludes comparisons between drugs of the NSAID class.
-
- The FDA proposed labeling does not adequately address the confounding effects of aspirin use, a non-selective NSAID, on upper GI outcomes and cardiovascular (CV) safety analyses. Such effects are quantitatively substantial, obscure the treatment effects of celecoxib per se, and introduce differential bias between treatment groups. The presentation of the non-aspirin analysis is both medically meaningful and allows for reasonable comparison between drugs of the NSAID class.
 - The analysis of hematocrit and hemoglobin, which was requested by the FDA, is not addressed in the FDA proposed label. This analysis is medically meaningful, and comparisons between treatment groups are consistent across all analyses (by aspirin use or disease type). Moreover, such information has been included in other NSAID labels. The absence of such information deprives the practitioner of important safety information and is inconsistent with the draft Guidance for Industry on Clinical Studies Sections of the label.

To date, the Division has declined to include the “combined endpoint” of symptomatic ulcers and ulcer complications in the labeling (relative to CELEBREX, diclofenac and ibuprofen), primarily on the basis of certain underlying concerns regarding the statistical analysis plan for the data. Pharmacia believes that the Agency is placing “form over substance.” The safety data that Pharmacia seeks to add to the labeling involves data that was prospectively collected but not termed a co-primary or secondary endpoint nor prespecified for combined analysis in the statistical plan. The Division has refused to include the symptomatic ulcer and ulcer complications data for the simple fact that the “words” specifying the combined endpoint were not described in the study protocol. However, Pharmacia would have done nothing differently in terms of data collection or analysis throughout the study if the words had been identified in the protocol. The data is thus robust, valid and reportable in the labeling.

The current approach by the Division is especially troubling given the discussions with representatives of the Division before the advisory committee hearing that:

- The “combined endpoint” of symptomatic ulcers and ulcer complications was a clinically meaningful endpoint to assess serious upper gastrointestinal toxicity
- The analysis of the effect of aspirin was pre-specified and aspirin use affected the outcomes measured
- Nominal p-values obtained by non-primary analyses were robust as determined by statistical testing

To exclude such data is inconsistent with the Agency’s mission – that is, to protect the public’s health – and with the Agency’s historical record for prescription drug labeling, especially when dealing with safety information. Pharmacia is simply seeking the Agency's acknowledgement that informative censoring had an impact on the validity of the primary endpoint. Acknowledgement of the differential bias of informative censoring across treatment groups as well as agreement on the clinical meaningfulness of the combined endpoint should allow for a further discussion on how this data should be incorporated into the labeling.

II. SOUND PUBLIC POLICY SUPPORTS INCLUSION OF THE ROBUST CLINICAL STUDY DATA THAT PHARMACIA SEEKS TO ADD TO THE LABELING FOR CELEBREX

A. The General Policy Surrounding Labeling For Prescription Drugs Favors The Inclusion Of Information That Is Clinically Necessary For Physicians To Safely And Effectively Prescribe Products

The Agency has readily acknowledged the importance of the product labeling in providing accurate and complete information to physicians so they can make informed prescribing decisions. 21 C.F.R. 201.57 provides that the labeling of a prescription product “shall contain a summary of the essential scientific information needed for the safe and effective use of the drug.”

On December 22, 2000, the Agency issued a proposed rule concerning *Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels*. As the Agency aptly summarized: “The part of a prescription drug product’s approved labeling directed to health care practitioners (also known as its “package insert,” “direction circular,” or “package circular”) is the primary mechanism through which FDA and drug manufacturers communicate essential, science based prescribing information to health care professionals.” [65 Fed. Reg.81082]. The Agency further stated:

This information [labeling] is intended to help ensure that health care practitioners are provided with a complete and accurate explanation of prescription drugs to facilitate their safe and effective prescribing. Thus, the regulations require prescription drug labeling to contain detailed

information on various topics that may be important to practitioners. [65 Fed. Reg. 81083]

The Agency also recently released a draft guidance entitled *Guidance for Industry: Clinical Studies Section of Labeling for Prescription Drugs and Biologics – Content and Format*. In the introduction to that draft guidance, the Agency wrote:

The overriding objective in labeling is to provide the information that is most useful to prescribers in treating their patients. *In some cases, making the information in the CLINICAL STUDIES section of labeling more useful to prescribers could warrant significant departures from past labeling practices.* (emphasis added)

In terms of discussing endpoints, the draft guidance provides:

The CLINICAL STUDIES section should present those endpoints that are essential to establishing the effectiveness of the drug (or that show the limitations of effectiveness) and those that provide additional useful and valid information about the activities of the drug. Endpoints presented should be endpoints the Agency has accepted as evidence of effectiveness, or closely related endpoints that may be more easily understood by clinicians. When it would be informative, the CLINICAL STUDIES section can also discuss other endpoints that were shown to be affected by the drug and endpoints that would have been expected to be influenced by the drug, but were not.

The safety information that Pharmacia seeks to include here in the Clinical Studies section will be useful to practitioners because it will provide important clinical information related to ibuprofen, diclofenac, CELEBREX and concomitant aspirin use.

B. Representatives Of The Division, As Well As Advisory Committee Members, Have Recognized That Public Policy Favors The Inclusion Of The Full Range of the CLASS Clinical Study Information In The Labeling For CELEBREX

A review of the FDA's presentations during the Arthritis Advisory Committee hearing, as well as the statements from various Advisory Committee members during the hearing, further supports the inclusion of the information Pharmacia seeks in the labeling for CELEBREX. Indeed, throughout the Arthritis Advisory Committee discussions concerning both the CLASS and VIGOR² trials, representatives of the Division and the advisory committee members recognized that it would be poor public policy to fail to include the "combined endpoint" information (especially as it relates to the comparator NSAIDS studied), as well as the hematocrit and hemoglobin data, simply because of the rigid application of a statistical principle.

² The "VIGOR" study is the long-term outcomes study performed by Merck comparing Vioxx with Naproxen.

1. Presentations By Members of The Division During The Arthritis Advisory Committee Meeting Support Inclusion Of This Data In The Labeling For CELEBREX

As noted above, during the January 26, 2001 meeting between Pharmacia and the Agency prior to the Arthritis Advisory Committee meeting, representatives of the Division acknowledged that the combined endpoint of symptomatic ulcers and ulcer complications was a clinically meaningful endpoint to assess serious gastrointestinal toxicity, notwithstanding that it was not a pre-specified endpoint (although both individual elements were). Those representatives also acknowledged the importance of the hemoglobin and hematocrit data. Moreover, the FDA presentation to the Advisory Committee by members of the Division clearly recognized the clinical importance of the data that Pharmacia now seeks to include in the labeling for CELEBREX.

There is no doubt that one of the principle issues surrounding the FDA's presentation to the Advisory Committee was the fact that the CLASS study did not meet its primary endpoint. Pharmacia does not dispute this and has never tried to diminish this fact in any of the labeling it has requested from the Agency with regard to the CLASS study. However, the Company continues to believe, as set forth in the attached documentation, that it is statistically appropriate to analyze other scientifically rigorous endpoints and present that information in labeling, even when the result of the analysis of the primary endpoint is not statistically significant. Furthermore, given that the primary endpoint was subject to bias by informative censoring and the recognized medical and clinical significance to the combined endpoint data, it would be scientifically justifiable to include this information.

FDA made several statements during their presentation to the Advisory Committee on February 7, 2001. Certainly, it was clear in the presentation that Pharmacia did not meet the primary endpoint in the CLASS study and that the combined endpoint was not pre-specified in the statistical plan. However, FDA did make certain statements reflecting the importance of the combined endpoint data and its clinical significance and acknowledging that documentation of symptomatic ulcers was defined in the protocol. Furthermore, FDA stated that this endpoint (symptomatic ulcers) is important, and is clinically relevant.

Pharmacia now seeks to add this clinically important data to the labeling for CELEBREX. In the draft labeling proposed by the Company, there is full disclosure of the primary endpoint and the failure to reach statistical significance. As well, the Company presents the results for the combined endpoint for all treatments, namely CELEBREX. The combined endpoint data for _____ should be added to the labeling in the interest of full disclosure of clinically relevant information to practitioners. The information should be further presented to show the impact of aspirin use which is an important clinical and real world factor. In addition, the hemoglobin and hematocrit data is clinically relevant and should be provided in the labeling.

2. Certain Comments By Members Of The Arthritis Advisory Committee Support The Inclusion Of This Data In The Labeling For CELEBREX

The Advisory Committee meeting relative to the long-term safety studies for CELEBREX and VIOXX was held over a two-day period on February 7 and 8 2001. Data on the CLASS study was presented on the first day; VIOXX data on the second. While there was extensive discussion on that first day relative to CELEBREX, it was not until the second day that the committee members seemed to truly understand and appreciate the nuances of the data and the importance of allowing the CLASS safety data in the labeling. On the second day, the review of the VIGOR study showed clear positive GI safety data when comparing VIOXX to naproxen in patients with the combined endpoint of complicated and symptomatic ulcers in patients who were not on aspirin. The committee members then recognized that the CLASS study data in the same population with regard to the combined endpoint in non-aspirin treated patients also showed significant safety benefit compared to ibuprofen.

Pharmacia does not mean to imply that all members of the Advisory Committee agreed with the general principle that the combined endpoint data, as well as the hemoglobin and hematocrit data, should be included in the label. Rather, Pharmacia does believe there was a general sentiment, expressed by recognized experts, that it is appropriate to allow inclusion of the data which Pharmacia seeks to include in the labeling for CELEBREX.

The subject of statistical analysis was discussed repeatedly at the Advisory Committee Meeting during the second day, after the presentation of both the VIOXX and CELEBREX data. For example, Dr. Wofsy made a statement that simply because the CLASS study didn't rise to statistical significance with regard to the primary endpoint, this was in his view a technicality and distinguishing the two compounds "would not be a service to the public." (February 8, 2001 transcript page 189) From the Agency's perspective, Dr. DeLap clearly expressed the fact that the Agency could and should put this information into the labeling, notwithstanding the statistical issues: "I think, again that last thing I will say is that we aren't captive, I think, to p-values, to follow up on the last speaker's comment. *Although p-values are a good way of making decisions, they are not the only way. Again, I think if we feel that there is information that is relevant and important information we try to and include that.*" (February 8, 2001, page 203, emphasis added)

The importance of the composite endpoint information to prescribers was also articulated by Dr. Nissen during the second day of the Advisory Committee meeting as follows: "I think what we really need to do is to provide some kind of a balanced view of what the studies showed and then let the physicians use their clinical judgment to pick the agent they think makes the most sense for their individual patients." (February 8, 2001, transcript page 196)³

³ Similarly, Dr. Cryor noted on the first day of the meeting: "In prioritizing each of these endpoints, symptomatic ulceration versus complicated ulcers, I do, in fact, think clinically that symptomatic ulceration is a clinically meaningful endpoint and a clinically important endpoint, and this is one of the arguments that the sponsors have been bringing forth this morning. (February 7, 2001, transcript, page 163)

Likewise, the importance of the hematocrit and hemoglobin information in the labeling was also discussed at the Advisory Committee hearing. As stated in the FDA review, these results “may be as meaningful as the composite endpoint of complicated and symptomatic ulcers since large drops in hemoglobin and hematocrit predispose to clinically relevant outcomes such as myocardial infarction, arrhythmia, congestive heart failure and syncope as well as others.” (page 64 of FDA medical review) Omission of these data deprives the practitioner of information pertinent to the safe use of compounds in the NSAID class.

The Committee also recognized during the second day of the meeting, after better understanding the data from both outcomes studies and the broad-ranging implications of that data, that if the information concerning naproxen was allowed in the Vioxx labeling, then the information relative to ibuprofen should be allowed in the CELEBREX labeling.⁴ Dr. Wolfe stated that “in fairness to celecoxib....then divide their study- and show the table- you do it all the time in the PDR- and show the differences between celecoxib.”⁵ (February 8, 2001, transcript page 212). Similarly in reference to CELEBREX, Dr. Harris also reiterated that “I think too if I feel this way I would have wanted, actually, the same thing to be done for celecoxib because, again, these are two massive studies if we are going to report, then let us report the results such as they are.” (February 8, 2001, transcript page 201).

Thus, Pharmacia believes that the public comments of the advisory committee members – principally during the second day after the full presentation of the data from both studies -- support its position that omission of the combined endpoint is both inconsistent with standard labeling practice and, perhaps more importantly, deprives the practicing physician of important and relevant medical information. As set forth more fully in the attached documentation, the analysis of a key endpoint, such as combined complicated and symptomatic ulcers, has statistical validity, especially as both components were pre-specified in the study protocol.

C. Other FDA Approved Labels Support The Inclusion Of This Clinical Study Data

Support for inclusion of the present data in the labeling for CELEBREX is also derived from precedent. Initially, it is important to recognize that the combined endpoint is also the standard for the NSAID Warning template. All recently approved NSAID package inserts contain information on the incidence of symptomatic ulcers, perforated ulcers and bleeding ulcers (i.e., PUBs). Therefore, presentation of the new safety information relative to the combined endpoint from the CLASS trial is the only way the

⁴ Part of the rationale for this was based on the fact that the primary endpoint for the VIGOR study was basically the “composite endpoint” that Pharmacia is seeking to add to its labeling relative to ibuprofen. (See, e.g., February 8, 2001 Transcript, page 138, comment of Dr. Goldkind.)

⁵ Dr. Wolfe also noted that he felt a lot of the reason that certain results might not have been shown with CELEBREX was simply a result of study design. (February 8, 2001 Transcript, page 212). The study design was, of course, approved by the FDA and the Agency provided input into that study design and throughout the course of the study.

medical practitioner can make meaningful comparisons between CELEBREX and drugs of the NSAID class. Indeed, omission of the combined endpoint is thus inconsistent with standard labeling practice for NSAIDs.

In addition, the NSAID labeling template contains a Precaution about changes in hematocrit and hemoglobin, and routine monitoring of hematocrit and hemoglobin for patients on NSAIDs is a standard of care and is, in fact, recommended in the NSAID labeling template. For example, the current labeling for CELEBREX states that "[p]atients on long-term treatment with CELEBREX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss." Thus, it is improper for the Agency to fail to include this relevant safety information concerning the hematocrit and hemoglobin data from the CLASS study. Indeed, this is particularly troublesome, in that recent changes to labels for products such as Vioxx and Relafen (nabumetone) have allowed information in the form of chromium tagged red cell studies. These studies are much less clinically relevant than the CLASS study in that they simply involve limited numbers of healthy volunteers (generally less than 100/group) and the practical implication of these findings to patients is unknown. The CLASS study, on the other hand, was a real world study involving patients with osteoarthritis and rheumatoid arthritis and involved almost 8,000 patients, with standard clinical assessments.

It is Pharmacia's belief that the Agency has also allowed the insertion of non-primary endpoint data in the labeling for other products.

D. Concerns About Advertising/Promotion Issues Are An Inappropriate Red Herring If They At All Play Into The Agency's Decision To Preclude This Important Clinical Study Data From The Labeling

Representatives of DDMAC were at the first meeting that Pharmacia had with the Agency concerning the proposed labeling changes to the CELEBREX labeling and indeed a representative of DDMAC began the meeting by expressing concern about any promotional activity Pharmacia might undertake relative to the CLASS clinical data.⁶ The preferred solution here, if the Agency is concerned about possible future promotional activities, is not the suppression of valuable scientific information in the labeling.⁷ Instead, after the labeling change, if DDMAC has concerns with how Pharmacia is promoting the information, it has available regulatory enforcement actions to address

⁶ While Pharmacia believes that DDMAC may try to take the position that Pharmacia may not promote certain aspects of the CLASS data, Pharmacia does not accept that position as a matter of law, policy or regulatory interpretation.

⁷ Indeed, while the recent draft Guidance issued by the Agency on the *Clinical Studies Section of Labeling for Prescription Drugs and Biologics – Content and Format*, addresses advertising and promotional considerations with regard to data in the clinical studies section, it does not advocate the wholesale exclusion of relevant data simply because the Agency may have some concerns from an advertising and promotional standpoint. Rather, it simply reflects the common sense view that the language should not be promotional in tone. (This is not a departure from current practice, in that 21 CFR 201.56 already requires that the labeling be informative and accurate, and not promotional in tone.) The language proposed by Pharmacia for the labeling for CELEBREX certainly complies with this requirement.

those concerns; actions which DDMAC has not hesitated to use when it feels a sponsor is inappropriately promoting information that is inconsistent with the labeling.

III. DESIRED RESOLUTION

Pharmacia has attached a 4-column document (Attachment # 2) which includes labeling language proposed by FDA in three side-by-side columns with the company proposal in the final column. We continue to believe that the labeling changes -- as most recently reflected in our submission of April 30, 2001 -- reflect what should be in the labeling for CELEBREX as a result of the CLASS study. The full statistical and clinical support for this position is set forth in the attached document.

We believe the language requested by Pharmacia in the labeling for CELEBREX will provide the appropriate medical and clinical information to the prescriber to be able to truly understand and analyze the CLASS data. It allows the presentation of clinically meaningful data to a physician in a balanced manner.

In order to bring resolution, we would like to address the following items with Dr. J. Woodcock and formally request the presence of Dr. R. Temple at the meeting:

- 1) Inclusion of the combined endpoint data
- 2) Inclusion of the Celebrex alone data for the combined endpoint
- 3) Inclusion of the hematocrit and hemoglobin data
- 4) Appropriate presentation of the cardiovascular profile in the label

We look forward to these discussions and bringing resolution to these labeling negotiations.

Sincerely,



Richard N. Spivey, Pharm.D., Ph.D.

Senior Vice President,

Global Regulatory Affairs

Tel (908) 901-8837; Fax (908) 901-1924

cc: Dr. J. Woodcock
Dr. R. Temple
Dr. J. Bull

SEARLE

SEARLE
4901 SEARLE PARKWAY
ROCKVILLE, ILLINOIS 60077

August 28, 2001



SE8-009/c

SUPL NEW CORRESP

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)
201 Corporate Boulevard
Rockville, MD 20850

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

Dear Dr. Bull,

You are undoubtedly aware of the recently published paper by Mukherjee D, Nisen SE, and EJ. entitled "Risk of cardiovascular events associated with selective COX-2 inhibitors," *JAMA*. 2001;954-959. This article raises concerns of an increased risk of cardiovascular events in patients taking COX-2 inhibitors. The authors propose a pharmacologic hypothesis based on preclinical data to support the rationale for this concern. The article is based on previously published material from several COX-2 inhibitor trials (3 rofecoxib, 1 celecoxib) as well as a meta-analysis of patients participating in cardiovascular primary prevention trials (*Heart* 2001;85:265-271). For celecoxib, the only trial examined and analyzed was the Celecoxib Longterm Arthritis Safety Study (CLASS).

The authors admit that there is no detectable increased cardiovascular risk for celecoxib compared to the two most commonly used NSAIDs. As you know, the CLASS study has been the subject of intense scrutiny by FDA and was examined in public at an Arthritis Advisory Committee meeting held on February 7, 2001. The specific issue of cardiovascular safety was reviewed and it was determined that there was no statistical or clinically meaningful difference between celecoxib and comparator NSAIDs in this respect.

Cognizing the lack of any direct evidence implicating celecoxib, Mukherjee et al attempt to make comparisons across different databases. This exercise is flawed in several respects:

The authors did not provide an adequate measure for heterogeneity of data, a routine practice in performing a meta-analysis. There is one particularly troubling comparison involving a "placebo" population extracted from a disparate group of

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studies which were conducted for entirely different purposes. This is inappropriate at best, and potentially highly misleading. In addition, the authors confuse basic epidemiological parameters by comparing a proportion of cases (%) with an incidence rate expressed as events per 100 patient-years. Proportions and incidence rates are different, as the latter has a time component.

-) The authors made no effort to account for differences between the patient profiles of aspirin users and non users. Aspirin use can be a surrogate marker for cardiovascular disease. A patient may take aspirin because of being at cardiovascular risk, but can have that risk decreased because of the use of aspirin. Thus, cases need to be examined for cardiovascular profile, not just pooled together. If any, the only meaningful comparison would be between users of celecoxib only and non-aspirin users in the placebo group. Nevertheless, the authors compared a non-aspirin treated "placebo" group with a celecoxib group, some of whom were receiving cardioprotective doses of aspirin (22%), some not (78%) When more homogeneous groups are compared, "placebo" vs. celecoxib alone, the celecoxib annualized rate of heart attacks is 0.33%. This is lower than the incidence in the "placebo" comparison group (0.52%) cited. The authors also do not make any effort to ensure that the definition of cardiovascular events are homogeneous among trials (i.e. all myocardial infarctions categorized under similar definitions).

Moreover, we question the relevance of even including celecoxib in the discussion. It is also noteworthy that at no time is there a comparison of the patients receiving NSAIDs in CLASS to the "placebo" meta analysis group, perhaps the most meaningful comparison (flawed though it is).

-) The authors attempt to combine studies of several different drug comparators, as well as ignoring uncontrolled use of concomitant medications.
-) The authors cite spontaneous reports without reference to the context of patient exposure to the drug. Celecoxib prescriptions started the week ending on January 22, 1999 and rofecoxib's prescriptions on the week of May 28, 1999. The number of cases reported (99 for rofecoxib and 102 for celecoxib) have, therefore, to be placed in context of 14 months and 19 months of exposure, respectively.

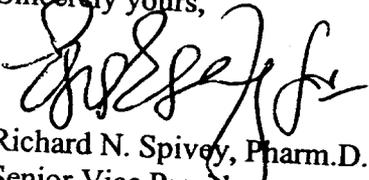
The flaws of the JAMA report are of such magnitude that it cannot be considered appropriate even for "signal-generation" purposes. As the FDA has recognized, there is no increased incidence of any cardiovascular signs or symptoms in the patients receiving high dose celecoxib in CLASS. For celecoxib patients the rates for hypertension, cerebrovascular accidents, edema and increased creatinine are either lower than or comparable to, those for the NSAID comparators (Attachment). We have also submitted replicate randomized clinical trial data to FDA which demonstrates that celecoxib does not increase mean systolic blood pressure in an elderly hypertensive population, whereas rofecoxib does.

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In conclusion, we believe that the data from the original NDA, the CLASS study, numerous post-marketing studies, and post-marketing surveillance fully support the cardiovascular safety of celecoxib. We will continue to monitor diligently for any new toxicity signal and, as always, we will provide additional data as it becomes available.

Sincerely yours,



Richard N. Spivey, Pharm.D. Ph.D.
Senior Vice President
Global Regulatory Affairs
(908) 901-8837

Enc.

**APPEARS THIS WAY
ON ORIGINAL**

SE1-010/c

8-1-01
8-2-01

SE8-009/ME

8-3-01
8-6-01

PHARMACIA

Pharmacia Corporation
P.O. Box 5110
Chicago, Illinois 60680-5110
tel 847.982.7000
www.pharmacia.com

August 3, 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



NDA 20-998
Re: Celebrex SNDA-009

SE 8-009/MR

Dear Dr. Bull,

In preparation for our proposed meeting of next week, we would like to provide a list of attendees:

Pharmacia:

Dr. P. Needleman, Senior Executive Vice President, Chief Scientific Officer Research and Development
Dr. R. Spivey, Senior Vice President, Global Regulatory Affairs
Mr. N. Wolf, Group Vice President of General Therapeutics, Global Prescription Business
Dr. S. Geis, Group Vice President, Clinical Research
Dr. D. Jordan, Head, Global Statistics and Programming
Dr. E. Essig, Associate Director, Global Regulatory Affairs

Pfizer:

Dr. M. Fletcher, Global Clinical Leader
Mr. M. Gavigan, Director/Team Leader, Celebrex Marketing

We understand that your office will provide further information about the meeting on Monday, August 6, 2001. During my absence from the office on Monday, I would ask that you please direct inquiries to Winifred Begley, Senior Director, Global Regulatory Affairs at 847-982- 8155 or Valerie Tews, our administrative assistant, at 847-982-7883.

We look forward to our discussion.

Sincerely,

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

EE/nb

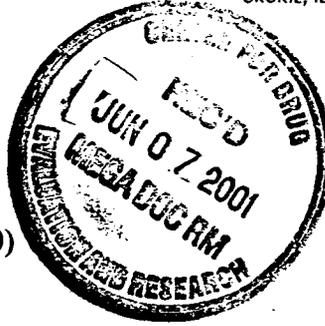
ORIGINAL

SEARLE

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

June 6, 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, Maryland 20850



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

Dear Dr. Bull:

Please find enclosed final minutes from our meeting of Friday June 1, 2001. If you have any comments, please contact the undersigned.

Sincerely,

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

Attachment

cc: Y. Kong, Pharm.D.

EE/jr

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SEARLE

NDA SUPPL AMEND
5E8-009/NC

May 29, 2001

Meeting materials for 6-1-01 mtg

SEARLE
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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, Maryland 20850



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

Dear Dr. Bull:

In anticipation of our meeting with the Division on June 1, 2001, we provide the attached document that includes:

- Introduction
- Prior Understandings Agreements with FDA
- Rationale for Full Inclusion of the Data on GI Outcomes and General Safety within the Clinical Studies Section
- Conclusion

At the meeting, we would like to give you a brief (15 minute) summary of CLASS and how it supports the requested labeling changes.

We look forward to a continued dialogue.

Sincerely,

Richard N. Spivey, Pharm.D., Ph.D.
Senior Vice President
Global Regulatory Affairs
(908) 901-8837

cc: Robert Temple, MD, Director,
Office of Medical Policy

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SEARLE

May 14, 2001

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Jonca Bull, M.D., Acting Director
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Office of Drug Evaluation V
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9201 Corporate Boulevard
Rockville, MD 20850



SE8-009/c

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

NDA SUPPL AMENDMENT

Dear Dr. Bull,

Pharmacia has recently completed the second of two comparative studies evaluating the cardiorenal safety of Celebrex versus rofecoxib in hypertensive patients. The first study entitled "A Double-Blind, Randomized, Parallel Group Comparison Study of the Safety of Celecoxib versus Rofecoxib in Hypertensive Patients with Peripheral Osteoarthritis taking Antihypertensive Medications" (Report # N49-00-06-149) was submitted to the IND on January 19, 2001.

In the second, recently completed comparative study entitled "A Double-Blind, Randomized, Parallel Group Comparison Study of the Safety of Celecoxib versus Rofecoxib in Treated Hypertensive Patients with Osteoarthritis" (Study Report # N49-01-06-181), the cardiorenal effects of 200 mg of celecoxib every day (QD) were compared with those of 25 mg of rofecoxib QD in approximately 1000 patients treated for 6 weeks. Results revealed that the proportion of patients reaching the systolic blood pressure endpoint (defined as a change from baseline >20 mm Hg and a value of >140 mm Hg) at any time was significantly ($p < 0.001$) lower in the celecoxib group (6.9%) as compared to the rofecoxib group (14.9%). Similarly, significantly more patients in the rofecoxib group experienced significant edema as compared to the celecoxib group, respectively 7.7% and 4.7% ($p = 0.045$). An abstract of this study is attached. A full copy of this study report is being concurrently submitted to celecoxib IND —

These studies provide convincing, replicate data which clearly demonstrate that there are differences in the cardiorenal profile between these two COX-2 inhibitors, supporting that there are molecule-based differences, and arguing against any general mechanism-based effect of COX-2 inhibition. Furthermore, these data provide strong support to molecule-based differences in cardiovascular effects as were observed across the two long-term outcomes trials recently completed for the two products.

NDA 20-998 S/009

Celebrex

May 14, 2001

Page 2

APPLICATION TO MARKET A NEW DRUG OR A NEW INDICATION
OR AN ANTIBIOTIC DRUG

Should you have any questions, please contact the undersigned.

Sincerely,



Richard N. Spivey, PharmD, PhD

Senior Vice President,

Global Regulatory Affairs

Tel: (908) 901-8837

Attachment: Synopsis of Final Report for a Double-Blind, Randomized, Parallel Group
Comparison Study of the Safety of Celecoxib vs Rofecoxib in Treated Hypertensive
Patients with Osteoarthritis (Study Report Number: N49-01-06-181)

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Number of Pages

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Commercial Information

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NDA SUPPL AMENDMENT

May 1st, 2001

SEARLE
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Ms. Jonca Bull
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

Re: Celebrex sNDA CLASS/S-009

Dear Dr. Bull,

Please find enclosed Pharmacia's revised Celebrex label dated April 30, 2001. It is provided in both hard and electronic versions. Also included is the supporting rationale and cited sections of the study protocols.

Sincerely,

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

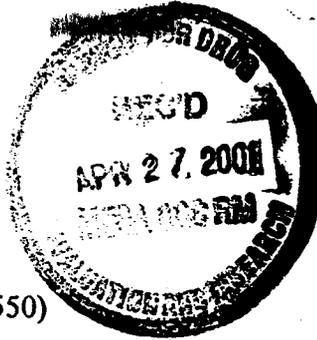
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SEARLE

April 26, 2001

Jonca Bull, M.D., Director
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SE8-009/k

NDA SUPPL AMENDMENT

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

Dear Dr. Bull,

Please refer to our submission of the revised label for Celebrex on Tuesday, April 24, 2001 and our upcoming meeting with the agency on Friday, April 27 at 2:00-3:00 pm.

As per FDA's suggestion, we have made a number of changes to the label, in particular to the Clinical Studies section. As per your recommendation, the following changes have been made:

1. The "Study Design" section has been modified to include wording compatible with the suggestions made by FDA in its April 18, 2001 version.
2. In the "Study Results" section, we have revised the data in Table 2 to reflect Kaplan-Meier (K-M) rates, with the inclusion of actual event numbers, as also proposed by FDA. With regards to Figure 3, we agree to the removal of this figure. As agreed at the meeting, we have revised Table 3, to incorporate the most important information with respect to withdrawals and serious adverse events originally included in FDA's proposed Tables 5 and 6 in the Adverse Reactions section of the label. The definition of "serious" has been included in the paragraph preceding this table.
3. Under "Endoscopic Studies", and upon your suggestion, we have shortened the introductory description of the studies and have removed Figure 5. As FDA stated in the pre-Advisory Committee meeting, the endoscopy data is important for a comprehensive understanding of the GI profile of this product.
4. Under "Use with Aspirin", we have included the K-M rates and actual event numbers for non-aspirin and aspirin users

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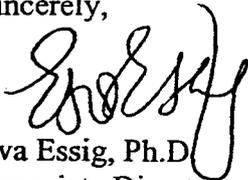
DECLARATION TO MARKET A NEW DRUG

5. Under "Warnings", as discussed previously, we have agreed to the reinstatement of the first three paragraphs of the template warning. However, in light of this addition, it is important to also include Celebrex rates (see Table 6) in order to allow prescribers to make informed judgments relative to Celebrex. A statement of the increased risk of events in the elderly and in those patients with a prior history of GI disease is also included. For "Advanced Renal Disease", we have maintained FDA wording with the inclusion of a clause "as with NSAIDs".
6. Under "Precautions, you agreed on 4/18/01 to the deletion of the second paragraph under "Laboratory Tests", beginning with "During controlled clinical trials.." For "Drug Interactions: Aspirin", we prefer that the reference be made to the Clinical Studies section- CLASS study as opposed to only the "Use with Aspirin" section. For "Geriatric Use", a full description of all information in this patient group is necessary per FDA guidance on Geriatric Use.
7. Under "Adverse Reactions", we have agreed to modify "controlled arthritic trials" to "original Celebrex NDA arthritis trials". Tables 5 and 6 from the FDA proposed label have been removed since this data is now in the Clinical Studies section.

While the above lists most of the changes, we do not think that a one hour meeting will allow for a discussion of all these items. Instead we propose that we focus on the CLASS study results, particularly Tables 2 and 3, in order to bring resolution to this important section of the label. If time permits, we would suggest then moving on to the Warnings section.

In addition, we have provided copies of the overheads we had hoped to present at the 4/18/01 meeting. These summarize our understanding of previous agreements on the CLASS data from the pre-Advisory Committee meeting with FDA and the Advisory Committee meeting itself.

Sincerely,



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

Attachments (slides)
EE/jr

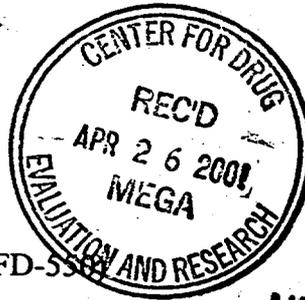
cc: Y. Kong, Pharm.D.

**APPEARS THIS WAY
ON ORIGINAL**

SEARLE

April 25, 2001

Jonca Bull, M.D., Director
Division of Anti-inflammatory, Analgesic
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SKOKIE, ILLINOIS 60077

SE 8-009 / MR

NDA SUPPL AMENDMENT

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

Dear Dr. Bull,

On April 24, 2001, we sent an electronic copy of the revised draft CLASS label to you. In addition we now provide three diskettes with a Word document with this most recent draft label revision in preparation for our meeting with the Agency on Friday April 27, 2001 to discuss revisions to the CLASS label.

Sincerely,

Wendy M. Essig

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

NAI yk

Attachments
EE/jr

cc: Y. Kong, Pharm.D.

FDA042501.doc

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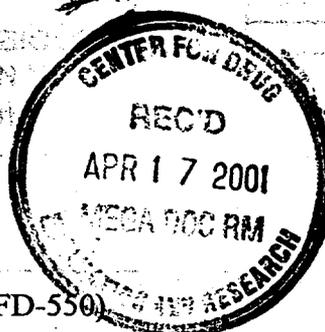
ORIGINAL

SEARLE

SK-8-0091

April 16, 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) S-009
NDA 20-998

Dear Dr. Bull,

Please refer to your approvable letter of April 12, 2001. Pursuant to 21CFR 314.110(a)(1) we hereby provide notice of our intent to file an amendment to this supplemental NDA.

Sincerely,

A handwritten signature in black ink, 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

SEARLE

SE8-009/mc

April 12, 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



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

Dear Dr. Bull,

Please refer to Searle's Supplemental New Drug Application (sNDA; S-009) to request modifications to the Celebrex product label based on results of the Celecoxib Long-Term Arthritis Safety Study (CLASS) submitted on June 13, 2000. Please also refer to our pre Advisory Committee meeting with the agency on January 26, 2001 (minutes submitted to the Division on February 1, 2001) and our submission of the revised product label for Celebrex on March 13, 2001.

We acknowledge receipt of FDA's proposed label for Celebrex faxed to Pharmacia/Searle on April 6, 2001. We would note that while further negotiation will be necessary, we are pleased to find that there are areas of the label in which we may readily reach an accord. Enclosed please find Pharmacia's revised label pursuant to a consideration of FDA's proposed label.

This revised label reflects many of the agency's suggested approaches as well as Pharmacia's understanding of agreements made at the pre-Advisory Committee Meeting (please see attached). Consistent with statements made in the FDA AAC briefing document, it was emphasized at this meeting that the study was well controlled and robust due to the choice of celecoxib dose, the study duration, the multiplicity of comparators, choice of endpoints, inclusion of both RA and OA patients and importantly inclusion of patient taking low dose aspirin. While it was accepted that the primary study endpoint was not met, the combined endpoint of symptomatic ulcers and ulcer complications was acknowledged as a clinically meaningful endpoint to assess serious upper gastrointestinal toxicity. In addition, the agency acknowledged that the analysis of the effect of aspirin was pre-specified in the protocol and that aspirin use affected the outcomes measured. Finally, we agreed that the nominal p values obtained by non-primary analyses were robust as determined by additional statistical testing.

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4/12/2001

To ensure that the product label reflects clinically relevant information required by the practicing physician, we strongly feel that the following data should be included in the Clinical Trials section:

We cannot envision how the study results can be accurately conveyed, and their implications to medical practice understood, without the inclusion of these data.

We look forward to a most productive meeting next week and feel that we can make significant progress towards an accord.

Sincerely,



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

Attachment

cc: Y. Kong Pharm. D.

EE/jr

**APPEARS THIS WAY
ON ORIGINAL**

SEARLE

June 12, 2000

6-19-00
NDA NO. 20-998 REF NO. 209 S.E.B.
NDA SUPPL FOR SLR SEARLE
1901 SEARLE PARKWAY
ROCKFORD, ILLINOIS 60077

Karen Midthun, 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, Maryland 20850



RE: NDA 20-998
Celebrex® (celecoxib)
Supplemental NDA

Dear Dr. Midthun:

Pursuant to 21 CFR 314.70, we are submitting a Supplemental New Drug Application for a labeling change to Celebrex® (celecoxib) and we are requesting a Priority Review.

Reference is made to Manual of Policies and Procedures (MAPP) 6020.3, entitled Priority Review Policy. A priority review classification is based upon whether "the drug if approved would be a significant improvement compared to marketed products in the treatment, diagnosis and prevention of a disease. Improvement can be demonstrated by, for example: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness in a new sub-population." Our data presented in this S/NDA justify the Priority classification referenced in item (2) above, and we hereby request a priority review classification.

Justification for Priority Review

Nonsteroidal anti-inflammatory drugs (NSAIDs) are an important component of the standard of care for osteoarthritis (OA) and rheumatoid arthritis (RA). These agents provide analgesic and anti-inflammatory effects via their inhibition of cyclooxygenase, the enzyme that catalyzes the conversion of arachidonic acid into prostaglandins and thromboxane, autacoids that mediate pain and inflammation. NSAIDs as a class of drugs, however, exhibit a common adverse effect profile. Many of these adverse effects are mechanism-based and result from the inhibition of prostaglandins and thromboxane: specifically, gastrointestinal (GI) toxicity, inhibition of platelet function, and renal dysfunction. Other common adverse effects of NSAIDs are less clearly mechanism-based, and include effects such as GI intolerance, hepatotoxicity, and dermatologic reactions.

ORIGINAL

Karen Midthun, M.D., Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
NDA 20-998
June 12, 2000
Page -2-

Several years ago, two distinct isoforms of COX were identified and designated COX-1 and COX-2. COX-1 is constitutively expressed in most tissues throughout the body, including the GI tract, kidney, and platelets. COX-2 is normally found in very low amounts in healthy tissue but is rapidly and highly induced in inflamed tissues by inflammatory mediators. The therapeutic benefits of NSAIDs are largely due to the inhibition of COX-2 at inflammatory sites, while the GI toxicity and platelet effects result from inhibition of COX-1. Because both COX-1 and COX-2 are expressed in the kidney, the mechanism of the renal effects of NSAIDs is somewhat complex, but when present, toxicity is largely COX-1-mediated.

This advance in understanding of the roles of the COX isoforms led to the development of celecoxib, a specific COX-2 inhibitor. The rationale behind the development of celecoxib was to provide comparable therapeutic benefit to NSAIDs via COX-2 inhibition, without the attendant COX-1-mediated toxicities inherent to the mechanism of NSAIDs. The data submitted with the original celecoxib New Drug Application (NDA 20,998) demonstrated that celecoxib is safe and effective for the relief of the signs and symptoms of both OA and adult RA. Celecoxib was also shown to be associated with statistically significantly lower incidences of endoscopically detected gastroduodenal ulcers compared to tested NSAIDs. However, the correlation between reduced ulcer incidences and the potentially lowered incidence of associated ulcer complications with celecoxib was not fully established. Therefore, the Celecoxib Long-term Arthritis Safety Study (CLASS N49-00-06-035_102) submitted in this supplemental NDA was designed to directly compare, in a prospective, controlled, double-blind trial, the incidence of clinically significant UGI events between celecoxib and comparator NSAIDs (diclofenac and ibuprofen).

NSAIDs exhibit a number of mechanism-based toxicities derived from their inhibition of COX-1, the principal such toxicity being GI in nature. NSAIDs cause symptomatic gastroduodenal ulcers and ulcer complications (bleeding, perforation, and obstruction) at a rate of two to four cases per 100 patient-years, the occurrence of ulcer complications alone being between one and two cases per 100 patient-years. Ulcer complications specifically are a substantial source of NSAID-associated morbidity and mortality, with an estimated 107,000 hospitalizations and 16,500 deaths attributable to this class of drugs annually in the U.S. The occurrence of ulcer complications is common to all NSAIDs, is dose-dependent, and has been observed even in patients taking low-dose aspirin for cardiovascular prophylaxis. The risk of NSAID-associated ulcer complications also appears to remain constant over time.

Karen Midthun, M.D., Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
NDA 20-998
June 12, 2000
Page -3-

Patients most at risk for NSAID-mediated ulcers and ulcer complications are the elderly, those with a history of GI ulcers or GI bleeding, and those with a history of cardiovascular disease. Other potential risk factors include general debility, smoking, alcohol, NSAID intolerance, concurrent use of corticosteroids or anticoagulants, and possibly concomitant infection with *Helicobacter pylori*.

NSAIDs may also cause small and large intestinal toxicity. NSAID enteropathy most often manifests as asymptomatic anemia, but may include intestinal ulcers, perforations, or strictures. Colonic involvement is, however, rare. The incidence of such events is difficult to determine, as these toxic effects often go unrecognized.

In addition to pathologic effects on the GI tract mucosa, NSAIDs also produce GI intolerance, which manifests as nonspecific symptoms such as dyspepsia, abdominal pain, and nausea. Because they often occur in the absence of ulcers or ulcer complications, these symptoms are poor positive predictors of serious GI toxicity. However, the occurrence of GI NSAID intolerance is a risk factor for more serious GI outcomes, indicating that GI tolerability and toxicity are interrelated.

Another mechanism-based toxicity of NSAIDs is platelet dysfunction. Because platelet aggregation depends on COX-1-mediated production of thromboxane, NSAIDs produce the potential for a bleeding diathesis by inhibiting COX-1 activity. This effect is evident clinically in the context of surgery or accidental injury and may contribute to GI toxicity as well. This property of NSAIDs also complicates the concomitant use of anticoagulant agents such as warfarin.

Renal dysfunction is also a side effect of chronic NSAID therapy. This may manifest as either acute alterations in renal function (e.g., a decline in glomerular filtration or sodium retention leading to congestive heart failure, edema, or hypertension) or more chronic syndromes (e.g., interstitial nephritis or papillary necrosis). The incidence of serious renal dysfunction is lower than that of GI toxicity. It has been estimated that the incidence of hospitalization for acute renal failure secondary to NSAIDs is on the order of 15 to 20 per 100,000 patient-years.

Karen Midthun, M.D., Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
NDA 20-998
June 12, 2000
Page -4-

Finally, NSAIDs are associated with a variety of adverse effects that are not mechanism-based but more likely idiosyncratic or immunologic in nature. The more common of these effects are hepatotoxicity and cutaneous reactions, although occurrence of more serious forms such as hepatic failure or exfoliative dermatitis (e.g., Stevens-Johnson syndrome) is rare.

The data from the CLASS study support the following conclusions for celecoxib 400 mg BID (4-times and 2-times the recommended doses for OA and RA respectively):

- Celecoxib is associated with a lower incidence of clinically significant upper GI events (CSUGIEs) and CSUGIEs/GDUs than NSAIDs;
- Celecoxib is associated with a diminished incidence of chronic decreases in hematocrit and hemoglobin, presumptively due to GI blood loss, compared with NSAIDs;
- No quantitative or qualitative changes were noted in the safety profile of celecoxib compared with that seen in previous celecoxib trials.
- Celecoxib is associated with improved GI tolerability relative to diclofenac;
- Celecoxib is associated with a diminished incidence of edema and hypertension relative to ibuprofen;
- Celecoxib is associated with a diminished incidence of clinically significant changes in BUN and creatinine compared with diclofenac; and
- Celecoxib is associated with a diminished incidence of clinically significant changes in liver function tests compared with diclofenac.
- No difference in the incidence of thromboembolic cardiovascular events was seen between celecoxib and NSAIDs.
- Celecoxib is associated with increased incidences of nonserious drug-related rash and pruritus compared with ibuprofen and diclofenac.

Therefore, based on the evidence presented, celecoxib (Celebrex®) "eliminates or substantially reduces a treatment limiting drug reaction" and meets the criteria for Priority review classification.

As agreed in our submission dated December 29, 1998 we undertook to collect data in the CLASS study on the effects of celecoxib on the acid-base status, including assessment of changes in serum bicarbonate, as a Phase 4 commitment. These data have been collected and analyzed and will be submitted as requested in your letter of December, 31, 1999 to the IND, with a cover letter to this NDA, and will be designated "Phase 4 Commitments".

Karen Midthun, M.D., Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
NDA 20-998
June 12, 2000
Page -5-

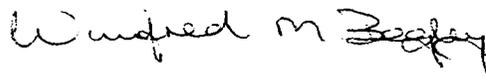
In addition to the CLASS study, which is the main report in this supplement, we have provided two pharmacokinetic studies N49-00-06-123 and N49-99-06-079. Study -123 is presented to establish bioequivalence of the diclofenac comparator used in the CLASS study compared to the marketed product. Study -079 is included to support a revised statement in the Overdose section of the proposed label.

In conformance with Title 1, Subtitle A of S. 830, the Food and Drug Administration Modernization Act of 1997, a User Fee check (I.D. #3940) in the amount of \$142,870.00 was received by _____ at Mellon Bank in Pittsburgh on 5-May-2000 at 8:50am.

In addition to the archival and review copies a desk copy of the submission (except for the pharmacokinetic section) has been sent directly to Dr. L. Goldkind.

Should you have any questions regarding the content of the S-NDA, please contact the undersigned at (847) 982-8155 or (847) 982-8090 (fax).

Sincerely,



Winifred M. Begley
Senior Director
Regulatory Affairs

Enc.
WMB/pl

**APPEARS THIS WAY
ON ORIGINAL**

SEARLE

June 21, 2000

Karen Midthun, 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, Maryland 20850

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077



NEW CORRESP

Nc

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

Dear Dr. Midthun:

The CLASS supplemental application as submitted 12-Jun-2000 was formatted in accordance with the Code of Federal Regulations, Title 21, Part 314.50. Both paper and electronic media were delivered at the time of submission. A full electronic rendition of the application was provided in Portable Document Format (PDF) formatted in accordance with the FDA Guidance, Guidance for Industry Providing Regulatory Submissions in Electronic Format - General Considerations (January 1999, IT 2) and Guidance for Industry Providing Regulatory Submissions in Electronic Format - NDAs (January 1999, IT3). The paper review copy includes the exact content of the electronic submission with the exception of Sections 11 and 12, Case Report Form Tabulations and Case Report Forms, respectively and patient endoscopic photographs. Sections 11 and 12 and images of endoscopic photographs were provided electronically only. Patient endoscopic videos were provided in the paper review copy only. For Sections 1 through 10 and Sections 13 through 19, both the paper and electronic formats were submitted to the archives. Two copies of a CD containing SAS transport files were provided in an envelope in Volume 1 of the archival copy contained in box 1 of 29.

A Digital Linear Tape (DLT) containing the electronic archive was provided in box 1 of 29 of the paper archival copy. The DLT was in a black case within a blue binder marked "Electronic Archive" and labeled with the Sponsor name, NDA No., product and submission date.

Please see attached letter dated 15-May-2000 to Randy Levin and IND outlining the S/NDA electronic submission format.

SEARLE

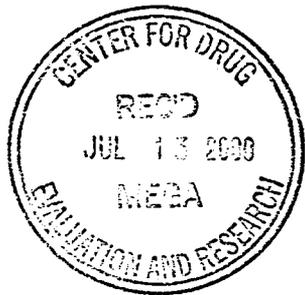
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July 12, 2000

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, Maryland 20850

NEW CORRESP



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

Dear Dr. Kong:

As requested, enclosed you will find 3 desk copies of volumes 9 and 10 of the Celebrex®
Class S/NDA.

Should you have any question, please contact the undersigned at (847) 982-8155 or
(847) 982-8090 (fax).

Sincerely,

Winifred M. Begley for:

Winifred M. Begley
Senior Director
Regulatory Affairs

Enc.
WMB/pl

ORIGINAL

SEARLE

July 17, 2000

Karen Midthun, 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, Maryland 20850

NEW CORRESP



RE: NDA 20-998
Celebrex® (celecoxib)
Supplemental NDA - CLASS

Dear Dr. Midthun:

Three desk copies of Volumes 9 and 10 of the Class S/NDA were delivered to Dr. Y. Kong as per her request of July 11, 2000. Please see attached cover letter for reference. NC

Should you have any questions, please contact the undersigned at (847) 982-8155 or (847) 982-8090 (fax).

Sincerely,

Winifred M. Begley
Senior Director
Regulatory Affairs

WMB/pl

ORIGINAL

SEARLE

NDA SUPPL. AMENDMENT

September 29, 2000

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

Bm

578-009

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,

With reference to a fax received September 26, 2000 regarding our supplement S-009 we enclose our response to the questions posed.

Please contact the undersigned if you require any further clarification.

Sincerely,

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

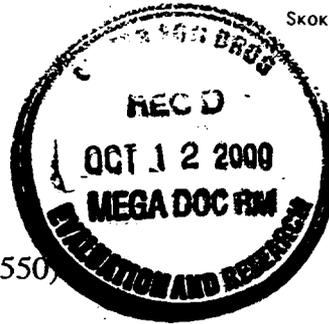
cc: Y. Kong Pharm. D.

**APPEARS THIS WAY
ON ORIGINAL**

SEARLE
4901 SEARLE PARKWAY
SKOKIE, ILLINOIS 60077

October 11, 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



NEW COPY
Ne

NDA 20-998
Celebrex® (celecoxib)

Dear Dr. Bull,

Attached is our response to the statistics reviewer question which was faxed to us on October 11, 2000.

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