

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 28, 2000

Re: NDA 20-998/S-009

Urgent

For Review

Please Comment

Please Reply

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● **Comments:**

Dear Winifred:

Please find below clarification requested regarding our information request for Celebrex AE narratives (faxed on December 10, 2000).

- The narratives are currently within a long Adobe document. They can be read; but they cannot be integrated with the rest of the SAS transport data.
- We need a simple ASCII or TEXT table containing two fields: the first one is for the unique patient identifier (the same unique patient identifier as the one the sponsor used for the SAS transport files) and the second for the narratives. The sponsor should prepare this table for all the narratives the sponsor included in the Integrated Summary of Safety.
- ◆ Provide as a special review aid a single file with the 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 is 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. Please see examples below.

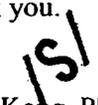
Example 1:

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 a infection of the right leg. She was treated with Cipro IV 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 if you need clarification, please contact me @ (301) 827-2090 or Ana Szarfman @ (301) 827-3209.

Thank you.


Yoon Kong, Pharm.D.

**APPEARS THIS WAY
ON ORIGINAL**

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**Division of Anti-Inflammatory, Analgesic,
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Center for Drug Evaluation and Research, HFD-550
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Pages: 3 (including cover page)

Date: January 3, 2001

Re: NDA 20-998/S-009

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

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● **Comments:**

Dear Winifred:

CARDIO-RENAL

Please provide a data-check of the following SAEs per 100 patient- years reported during CLASS with respect to ASA and non-ASA users.

For the renal SAEs, too few were reported to analyze according to the use of ASA. The table below summarizes the incidence of relevant cardiac SAEs according to the use of ASA.

Serious Adverse Events (SAEs) per 100 Pt-Yrs Reported During CLASS^a.

Adverse Event	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
<i>ASA Users</i>	N=882 517 Pt-Yrs	N=445 N=239 Pt-Yrs	N=412 249 Pt-Yrs
Cardiac SAEs			
Atrial Arrhythmias			
Arrhythmia Atrial	2 (0.4%)	0 (0%)	1 (0.4%)
Bradycardia	0 (0%)	0 (0%)	0 (0%)
Fibrillation Atrial	4 (0.8%)	1 (0.4%)	3 (1.2%)
Tachycardia	1 (0.2%)	0 (0%)	0 (0%)
Supraventricular			
Combined Atrial SAEs^b	7 (1.4%)	1 (0.4%)	4 (1.6%)
Angina			
Unstable Angina	6 (1.2%)	4 (1.7%)	0 (0%)
Angina Pectoris	3 (0.6%)	5 (2.1%)	4 (1.6%)
Coronary Artery Disorder	11 (2.1%)	2 (0.8%)	5 (2.0%)
Combined Anginal Disorders	20 (3.9%)	11 (4.6%)	9 (3.6%)
Myocardial Infarction	18 (2.9%)	2 (0.8%)	7 (2.8%)
Thrombophlebitis Combined ^d	0 (0%)	2 (0.8%)	1 (0.4%)
<i>Non-ASA Users</i>			
Cardiac SAEs			
Atrial Arrhythmias			
Arrhythmia Atrial	0 (0%)	0 (0%)	0 (0%)
Bradycardia	2 (0.1%)	0 (0%)	0 (0%)
Fibrillation Atrial	5 (0.3%)	1 (0.1%)	0 (0%)
Tachycardia	2 (0.1%)	0 (0%)	0 (0%)
Supraventricular			
Combined Atrial SAEs^b	9 (1.7%)	1 (0.1%)	0 (0%)
Angina			
Unstable Angina	2 (0.1%)	0 (0%)	0 (0%)
Angina Pectoris	1 (0.1%)	0 (0%)	0 (0%)
Coronary Artery Disorder	8 (0.4%)	3 (0.4%)	0 (0%)
Combined Anginal Disorders	11 (2.1%)	3 (0.4%)	0 (0%)
Myocardial Infarction	8 (0.5%)	2 (0.2%)	2 (0.2%)
Thrombophlebitis Combined ^d	8 (0.4%)	4 (0.5%)	0 (0%)

a. Data from electronic data submission, Appendix 2.9.4 and 2.9.3.

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.

PHARMACOKINETICS

Also, please provide the following information regarding the SAS data set and program codes provided regarding our November 29, 2000, information request regarding Study N 499-99-02-123.

Subject	gender	age	wt	treatment	sequence	period	AUCt	AUCinf	Cmax	Tma
1	F	22	52	S	A	1				
1	F	22	52	V	A	2				
1	F	22	52	V	A	3				
1	F	22	52	S	A	4				

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**APPEARS THIS WAY
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If you have any questions or if you need clarification, please contact me @ (301) 827-2090.

Thank you.

Yoon Kong, Pharm.D.

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Fax



**Division of Anti-Inflammatory, Analgesic,
Ophthalmic Drug Products**
Center for Drug Evaluation and Research, HFD-550
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From: Yoon Kong, Pharm. D.

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Phone: (847) 982-8090 8155

Phone: 301-827-2090

Pages: 1 (including cover page)

Date: January 9, 2001

Re: NDA 20-998/S-009

Urgent For Review Please Comment Please Reply Please Recycle

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● Comments:

Please provide a response to the following question from our pharmacokinetics reviewer.

The *in vitro* dissolution results show that CLASS 2 diclofenac tablets did not dissolve in the acidic medium (0.1N HCl) but dissolved slower than Voltaren® tablets in a ———. On the other hand, the *in vivo* study shows faster absorption of diclofenac from the former tablets resulting in a shorter mean Tmax compared to Voltaren tablets. Please explain these differences observed.

Also, how do the dissolution profiles of the 2 diclofenac formulations compare in a dissolution medium with a ———

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

Thank you.

Yoon Kong, Pharm.D.

YK

Fax



**Division of Anti-Inflammatory, Analgesic,
Ophthalmic Drug Products**
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
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Pages: 1 (including cover page)

Date: January 18, 2001

Re: NDA 20-998/S-009

Urgent

For Review

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● **Comments:**

Dear Winifred:

In the datasets of UGI adverse events and CSUGIEs there are subjects who have an UGI adverse event listed as occurring after the CSUGIE. Please explain.

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

Thank you.


Yoon Kong, Pharm.D.

Fax



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

Sent on 1-23-01

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:** January 23, 2001

Re: NDA 20-998/S-009

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● **Comments:**

Dear Winifred:

Please provide a list of all subjects with GI symptoms that went on to have CSUGIEs and GDUs with the patient ID and case numbers (these are the cases used to define a relative risk of CSUGIEs associated with GI symptoms). Also, please include in this list, the date used for the GI symptoms and CSUGIE date used for each case.

Please provide the above requested information as soon as possible.

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

Thank you.

Yoon Kong, Pharm.D.

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/s/

Yoon Kong
1/23/01 09:30:40 AM
CSO

Please review and sign off so that can fax immediately to sponsor. Thanks.

Lawrence Goldkind
1/23/01 10:26:09 AM
MEDICAL OFFICER

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: Eva Essig, Ph.D.

From: Yoon Kong, Pharm. D.

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Phone: (847) 982-8980

Phone: 301-827-2090

Pages: 5 (including cover page)

Date: April 24, 2001

Re: Guidance for Industry- Resubmissions (Class 1 and Class 2)

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

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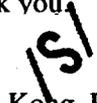
● **Comments:**

Dear Eva,

Per our phone conversation earlier this morning, please find attached information regarding "Resubmissions in Response to Action Letters", which can be found in the Guidances for Industry website (<http://www.fda.gov/cder/guidance/index.htm>).

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

Thank you,


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: Eva Essig, Ph.D.

From: Yoon Kong, Pharm. D.

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Pages: 26 (including cover page)

Date: May 10, 2001

Re: NDA 20-998/S-009

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

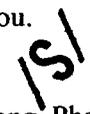
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● **Comments:**

Persuant to our telephone discussion earlier this morning, please find attached our most recent proposed draft labeling regarding Celebrex-CLASS.

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

Thank you.


Yoon Kong, Pharm.D.

Number of Pages

Redacted 25



Draft Labeling
(not releasable)

MEETING MINUTES

MEETING DATE: June 1, 2001 **TIME:** 3:30 p.m.-5 p.m. **LOCATION:** CORP S300

sNDA#: 20-998/S-009

Briefing Document Submission Date: May 29, 2001

Additional preparation documents: April 26, 2001 (Searle's most recent proposed labeling to date of June 1, 2001 meeting); May 10, 2001 (Agency's most recent proposed labeling to date of June 1, 2001 meeting)

DRUG: Celebrex® (celecoxib capsules) Capsules, 100 mg and 200 mg

SPONSOR/APPLICANT: G.D. Searle/Pharmacia

TYPE of MEETING: Labeling

FDA PARTICIPANTS:

Jonca C. Bull, M.D.	Acting Division Director, DAAODP
Robert Temple, M.D.	Associate Director for Medical Policy
Lawrence Goldkind, M.D.	Medical Team Leader
Joel Schiffenbauer, M.D.	Medical Officer
Laura Lu, Ph.D.	Statistics Reviewer
Stan Lin, Ph.D.	Statistics Team Leader
Yoon Kong, Pharm.D.	Project Manager

INDUSTRY PARTICIPANTS:

Searle/ Pharmacia

Dr. Philip Needleman	Research and Development, Head
David Jordan	Statistician
Dr. Richard Spivey	Regulatory Affairs
Dr. Steve Geis	Clinical Research
Winifred Begley	Senior Director, Regulatory Affairs

Pfizer

Michael Gavigan	Commercial
Dr. Mark Fletcher	Global Clinical Leader

MEETING OBJECTIVES: To discuss outstanding issues regarding labeling for this sNDA resubmission, particularly with respect to full inclusion of the data on the CLASS (Celecoxib Long-Term Safety Arthritis Study) GI outcomes and general safety within the "Clinical Studies" section.

Prior to discussion, Dr. Geis gave a brief slide presentation of CLASS (large GI outcomes study) and how it supported their requested labeling changes (see attachments).

DISCUSSION:

Dr. Temple asked the sponsor their rationale for looking at the non-Aspirin users. The sponsor indicated that it was pre-specified and that they were interested in looking at the impact of aspirin use on GI safety outcome. Also, sponsor noted that there was a an effect which could be detected from those patients who took low-dose aspirin; sponsor stated that non-Aspirin users represent the general public and this information would be beneficial if it were to be included in the labeling so as to better assist the prescribing physician.

Dr. Temple indicated that selectively presenting certain data from the CLASS trial, such as Aspirin and non-Aspirin use, would not be appropriate to include in the labeling, given the failure of the primary endpoints and the inconsistencies between comparators in the subpopulation analysis based on Aspirin-use.

Dr. Temple emphasized that the sponsor did not meet the primary endpoints, hence, comparative claims could not be made. Dr. Temple stated that typically, in order to make a comparative claim, the claim should be tested in two, adequate, well-controlled trials with the fulfillment of successfully meeting the designated, primary endpoints. Dr. Temple additionally noted that single, large, outcome studies may be adequate when the results are clear and robust.

Dr. Temple reiterated to the sponsor the absolute need for testing against stringent criteria to establish a major, comparative claim.

The sponsor indicated that full disclosure of data generated from the CLASS trial should be shown with respect to thromboembolic events to demonstrate that there are no statistical differences between the adverse events from the original Celebrex submission and the CLASS trial submission. Given this, the sponsor wants to dispel the general hypothesis currently circulating in the scientific world that COX-2 inhibitors increase the incidence of thromboembolic events.

Dr. Temple responded that the CLASS trial was not powered to demonstrate comparability at this safety endpoint (e.g. thromboembolic events). Thus, Dr. Temple concluded that statistical inferences could not be made.

The sponsor proposed separating the **Adverse Event** tables for the CLASS trial based on Aspirin use. Dr. Temple again stressed that the sponsor could not make comparative claims by separating out the Aspirin and non-Aspirin users. Dr. Temple suggested that further internal discussion would be considered regarding this issue.

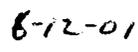
Dr. Temple indicated that the CLASS trial was one of the most instructive NSAID studies conducted in contemporary science. Moreover, Dr. Temple suggested that another trial, whether it be an active or non-inferiority trial with complicated ulcers using treatment regimens which currently work may provide valuable information (e.g., Celebrex vs. Cytotec/NSAIDs).

ACTION ITEMS:

1. The Agency would internally discuss the following issues before taking an action:
 - separation/breakdown of Aspirin vs. non-Aspirin users and where to place ~~in the labeling~~ **in the Adverse Events section of the labeling**
 - display of hematocrit and hemoglobin information in the **Adverse Events** of the labeling
 - combined endpoints (e.g., complicated/symptomatic ulcers)
2. The Agency would issue an action by the June 12, 2001, due date.



Yoon Kong, Pharm.D.
Project Manager

Concur:  

Jonca Bull, M.D.
Acting Division Director, DAAODP

Attachments: Sponsor's slide presentation (10 slides).

**APPEARS THIS WAY
ON ORIGINAL**

NDA Conclusions: GI Effects of Celecoxib

- Incidence of endoscopic ulcers
 - Similar to placebo
 - Lower than NSAIDs
- Incidence of ulcer complications
 - Lower than NSAIDs

Clinical Relevance

- The generalizability of the ulcer complications analysis was uncertain:
 - About 40% of patients were ulcer free by endoscopy at study entry
 - Most studies were 3 months in duration

Rationale for CLASS

- Rigorous assessment of upper GI safety of celecoxib:
 - Using clinically relevant outcomes
 - In patients that fully represent the intended population
 - With chronic exposure

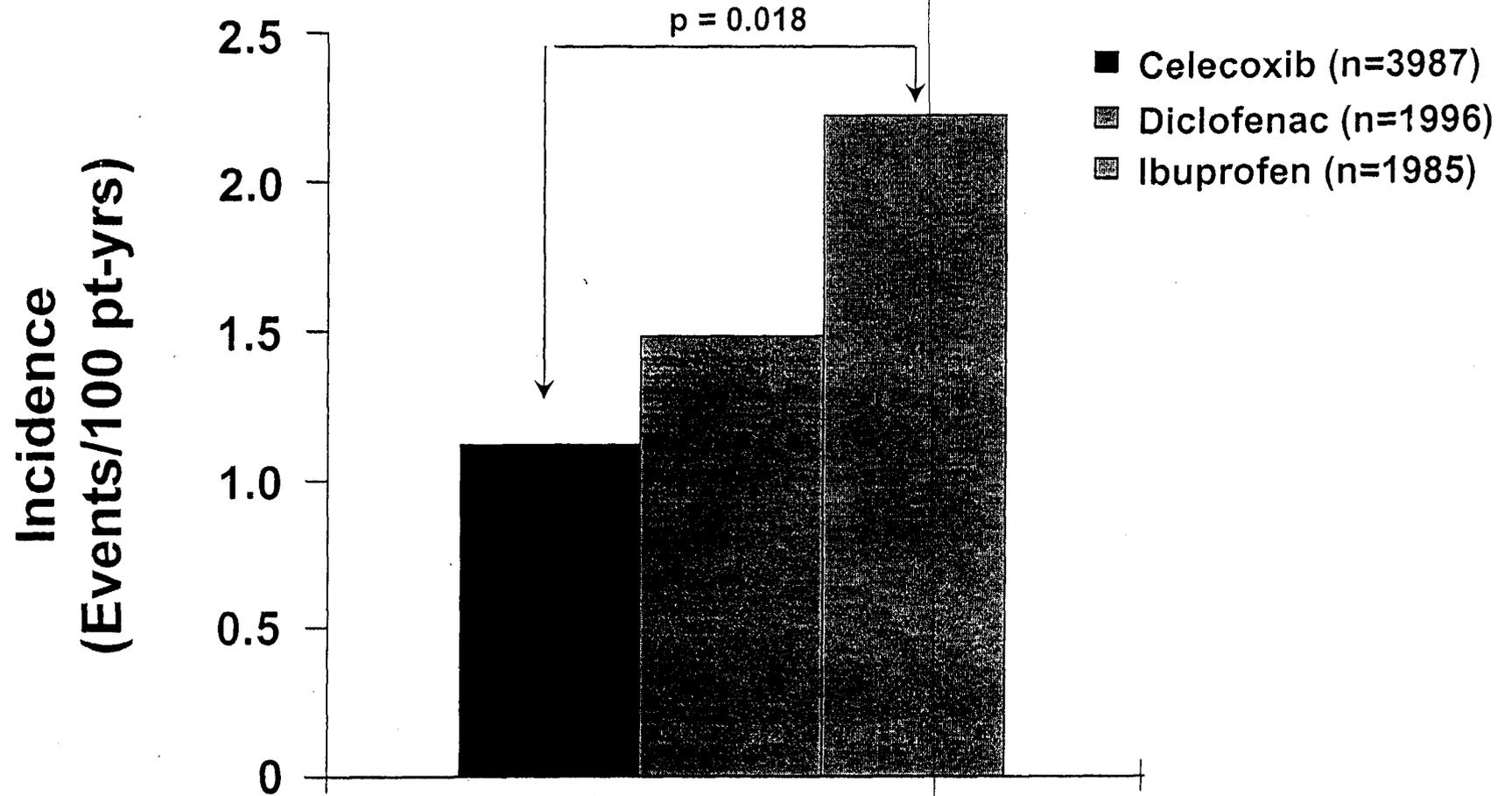
Data Important to Physicians

- High dose celebrex associated with a lower incidence of symptomatic ulcers/ulcer complications compared to ibuprofen
- Effect greatest in patients not taking ASA
- Celecoxib is not associated with an increased incidence of MI relative to NSAID comparators

CLASS GI Safety Analysis

- Symptomatic ulcer/ulcer complications are clinically meaningful and statistically the most appropriate GI endpoint
 - Ulcer complication analysis affected by informative censoring
 - treatment of GI symptoms prohibited
 - endoscopy rates ~2 fold higher than expected
 - withdrawal of patients with symptomatic ulcers required

Symptomatic Ulcer Rate



NDA: Cardiovascular Adverse Events

% of Patients

	<u>Placebo</u> <u>(n=1864)</u>	<u>Celecoxib*</u> <u>(n=6376)</u>	<u>NSAID</u> <u>(n=2768)</u>
All Patients			
Myocardial Infarction	0.11	0.16	0.07
Cerebrovascular	0.11	0.09	0.07
Non-ASA Users			
Myocardial Infarction	0.06	0.05	0.04
Cerebrovascular	0.06	0.05	0.08

* Doses 25-400 mg BID

Incidence (%) of MI

	<u>Celecoxib</u>	<u>Diclofenac</u>	<u>Ibuprofen</u>
CLASS (p = NS)			
All Patients	0.5	0.3	0.5
Non-ASA Users	0.2	0.1	0.1

Incidence (%) of MI

	<u>Celecoxib</u>	<u>Diclofenac</u>	<u>Ibuprofen</u>
CLASS (p = NS)			
All Patients	0.5	0.3	0.5
Non-ASA Users	0.2	0.1	0.1

	<u>Rofecoxib</u>	<u>Naproxen</u>
VIGOR (p < 0.05)		
Non-ASA Users	0.5	0.1

MEETING MINUTES

MEETING DATE: September 13, 2000 **TIME:** 11 a.m.-12 noon **LOCATION:** CORP S300

IND#: _____ **Meeting Request Submission Date:** July 11, 2000
Briefing Document Submission Date: July 21, 2000
Additional preparation documents: August 4, 2000 (individual study tables from 3 European pain trials)
 August 8, 2000 (draft table of contents)

DRUG: Celebrex® (celecoxib capsules) Capsules, 100 mg and 200 mg

SPONSOR/APPLICANT: G.D. Searle

TYPE of MEETING: pre-NDA

FDA PARTICIPANTS:

Robert Delap, M.D., Ph.D.	Office Director, Office of Drug Evaluation V
Jonca Bull, M.D.	Acting Division Director, DAAODP
James Witter, Ph.D., M.D.	Medical Officer Reviewer
Lawrence Goldkind, M.D.	Medical Team Leader, Anti-inflammatory
Kent Johnson, M.D.	Medical Officer
Robert Osterberg, R.Ph., Ph.D.	Acting Pharmacology/Toxicology Team Leader
Laura Lu, Ph.D.	Statistics Reviewer
Yoon Kong, Pharm.D.	Project Manager

INDUSTRY PARTICIPANTS:

<u>Searle</u>	
Winifred Begley	Senior Director, Regulatory Affairs
Dr. A. Brugger	Senior Director, Clinical Research
O. Coughlin	Senior Project Director, Project Management
Dr. S. Geis	Vice-President, Clinical Research
J. Gyzen	Director Electronic Submissions
M. Novak	Assistant Director, Clinical Research
J. Oidtman	Senior Director, Global Regulatory Operations
Dr. N. Ridge	Associate Director, Clinical Research
Dr. Y.F. Yang	Senior Statistician
Dr. W. Zhao	Director, Clinical Statistics

IND ———
Celebrex- other indications
Pre-NDA meeting
9/13/00
Page 2

Pfizer

S. Cristo
Dr. W. Frost
Dr. L. Loose
Dr. M. Wahba

Associate Director, Drug Regulatory Affairs
Senior Associate Director Therapeutic Area Leader
Director, Clinical Development
Senior Associate Director, Clinical Development

MEETING OBJECTIVES: To discuss sponsor's questions to Agency submitted in meeting package dated July 21, 2000, with respect to expanding indications for Celebrex for management of acute pain, treatment of primary dysmenorrhea, and relief of the signs and symptoms of ankylosing spondylitis.

QUESTIONS for DISCUSSION:

Proposed Organization and Content of Celecoxib sNDA ISE

1. Is the overall organizational plan of the ISE satisfactory?

FDA indicated that it appears to be reasonable.

2. In presenting the data for the management of acute pain and treatment of primary dysmenorrhea, we plan to resubmit the pain studies summarized in the original celecoxib NDA as well as include pain studies completed subsequent to the original NDA submission. Is that acceptable?

FDA indicated that it appears acceptable to submit and stated that the adequacy of the data will be a review issue.

3. In presenting efficacy results for the management of acute pain and treatment of primary dysmenorrhea, the following efficacy measurements will be discussed in the text of the report:

- Time specific PID (categorical), PR and PRID
- SPID and TOTPAR
- Time and percent of patients with onset of analgesia
- Time and percent of patients who took rescue medication
- PPR and PPID (categorical)

IND _____
 Celebrex- other indications
 Pre-NDA meeting
 9/13/00
 Page 3

The primary efficacy analysis will utilize the LOCF method of imputing missing values. Analyses utilizing the BOCF and WOCF methods of imputation will also be provided. Is this acceptable?

Following points made by the FDA:

- **Generally, favors the ITT with LOCF (given primacy in analyses) analyses. Sponsor agreed with this approach.**
- **Considers the BOCF and WOCF as meaningful secondary analyses. Sponsor stated that these types of analyses would be contained in the appendices of the application.**
- **Pre-planned statistical analyses should be identified for each study. Any modifications/adjustments made, should be described, and the impact of such changes (e.g., need for statistical adjustments) should be described.**
- **Data presented in the ISE is an efficient way to look at all studies. Any important analyses and amendment to the initial design should be noted in the ISE.**
- **Consistency of results and endpoints across studies will be important.**

Additional FDA Comments:

- 1) **FDA asked whether the primary endpoints that sponsor selected would be the same for all studies. Sponsor informed FDA that this would be the case, except for the primary dysmenorrhea studies.**
 - 2) **FDA asked if sponsor is planning _____ . In study 139, there was an _____ . The sponsor informed FDA that the current sNDA will only include the celecoxib capsule formulation, but they will follow up with this in more detail.**
- 4. The following efficacy measures for the management of acute pain and treatment of primary dysmenorrhea will also be included in the appendices of the ISE:**
- **Time and percent of patients with onset of perceptible pain relief**
 - **Time and percent of patients with meaningful pain relief**
- Is this acceptable?**

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FDA indicated that this appears to be acceptable.

5. Analyses of pooled results for the management of acute pain and treatment of primary dysmenorrhea will be conducted to assess the following subgroups:

- Gender
- Ethnic origin
- Age

Is this acceptable?

- This is generally acceptable, however, the sponsor would need to provide additional data to support appropriateness of pooling of results across different studies.

FDA asked sponsor to confirm why they would want to pool data from individual studies, in addition to analyzing each individual study. Sponsor noted that they would include their justification for pooling data within the ISE. According to sponsor, pooling would provide better estimation of subgroup effects. The sponsor stated that studies 085 and 086 are similar in study design and population and there is no interaction in terms of efficacy and demographics, hence, pooling of data is valid in this case. Also, sponsor explained further that they would assess the data from the dental and post-operative studies separately.

At this juncture in the meeting, sponsor presented slides (slides #16 and #17- see attachments).

Sponsor asked whether they could pool data by similar study design using the same population. FDA stated that sponsor could pool very similar studies for subgroup and safety analyses. However, primary analyses cannot be pooled.

- Expressed concern with sponsor using results of pooled data to support a labeling claim.
- It would be problematic if sponsor finds analysis of primary endpoints not to be successful, and then would turn to the subgroup analysis as primary vs. supportive. Sponsor assured FDA that they did not intend to claim the subgroup analysis in terms of pooled data, but would probably use this as supportive evidence.
- Sponsor should provide a justification for pooling data and define how this data varies from primary study results.

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➤ Sponsor should be attentive to gender analysis in analgesia (e.g., differences in gender in pain studies). Sponsor indicated that they believe that have data that differs across models, studies and groups.

6. In the context of the extensive celecoxib OA and RA clinical data, we (Searle) believe that one adequate and well-controlled six-week trial in patients with ankylosing spondylitis provides substantial evidence of efficacy in the treatment of ankylosing spondylitis. The following primary measures of efficacy will be discussed in the text of the ISE:

- Change from Baseline in the Global pain intensity (VAS)
- Change from Baseline in the Bath Ankylosing Spondylitis Functional Index (BASFI); the BASFI is a measure of functional impairment utilizing a ten item questionnaire Is this acceptable?

➤ This is not sufficient for the following reasons: a) there is uncertainty regarding the most clinically relevant endpoints b) further discussion is required due to this fact.

➤ The study presented appears to be a good first study, but emphasized that a longer duration study is needed (e.g., 12 weeks duration).

Sponsor inquired what types of endpoints the FDA had in mind. Sponsor indicated that they would be using global pain intensity, Bath Ankylosing Spondylitis Functional Index as primary plus other secondary endpoints (see attachments- slide #11). FDA informed sponsor that any primary endpoint strategy should try to balance the older (e.g., NY criteria) with newer endpoints (e.g., JJ Anderson et. al) for AS.

FDA noted that AS is a chronic disease and requires it to be studied in a chronic way (e.g., minimum of at least 3 months). Sponsor asked whether they would need a 12-week study for efficacy or safety. FDA responded that they would need to have both. Sponsor also inquired if they collected the right information, would it matter whether they used primary or secondary endpoints. FDA pointed out that we would need to see information first to determine its meaningfulness. Sponsor also asked if one additional dose-ranging study of a 12-week duration would be sufficient. FDA explained that at this juncture, we could not comment without having a complete package to review. FDA recommended that sponsor consider requesting an end-of-phase 2 meeting.

Proposed Organization and Content of Celecoxib sNDA ISS

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1. Is the overall organizational plan of the ISS satisfactory?

FDA stated that this appears to be acceptable.

2. In presenting the safety data, we plan to resubmit the pain studies summarized in the original celecoxib NDA as well as include pain studies completed subsequent to the original NDA submission. Is that acceptable?

FDA stated that this appears to be acceptable.

3. In discussing the safety data we plan to —

The following European studies do not lend themselves to pooling and will be discussed individually:

- European post-surgical pain study
 - European narcotic-sparing post surgical pain study
 - European low back pain study
- Is this acceptable?

FDA stated that this appears to be acceptable.

4. Analyses will be conducted in the following subgroups:

- Gender
 - Ethnic origin
 - Age
- Is this acceptable?

FDA stated that this appears to be acceptable.

Labeling

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1. We (Searle) are seeking approval for the management of acute pain, the treatment of primary dysmenorrhea and the treatment of _____

2. In the adverse event section we plan to discuss adverse events encountered in the studies of primary dysmenorrhea in a separate section. This section would be similar to the FAP adverse event section. A draft of the language is: "Adverse events from the controlled trials in primary dysmenorrhea: The adverse event profile reported for the 300 patients with primary dysmenorrhea enrolled in the randomized, controlled clinical trials was similar to that reported for patients in the arthritis controlled trials. The crude incidences of the following events that frequently accompany primary dysmenorrhea are listed in the following table.

With respect to labeling, FDA indicated that we would need to view the data before labeling would be established for the use of Celebrex for various indications. These issues are primarily review issues.

FDA also pointed out that we would examine carefully the data presented and tries to determine the most appropriate means of conveying this information via the labeling of the drug product.

As mentioned earlier in this discussion, FDA would like to discuss such issues in an EOP2 meeting in the near future for sponsor's drug development plan for the _____ indication that sponsor is seeking.

Sponsor gave a slide presentation with the remaining time left in the meeting (see attachments).

ACTION ITEMS:

1. Sponsor will provide slides that were presented in the meeting.

2. FDA will provide _____

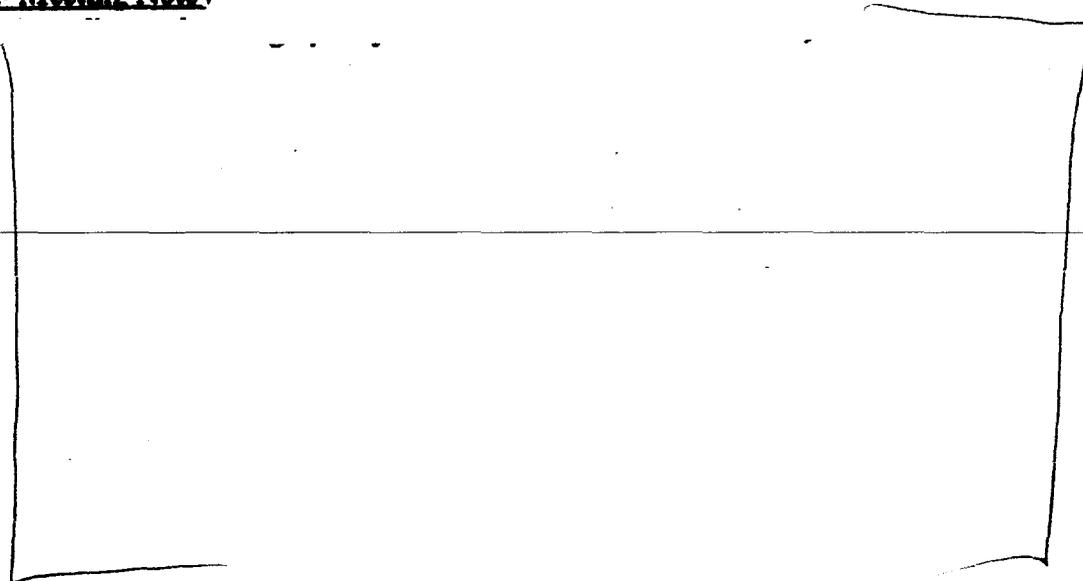
Yoon Kong, Pharm.D.
Project Manager

Concur: Erica Bull, M.D.
Acting Division Director, DAAODP

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Attachments: Sponsor's slide presentation (NDA 20-998/S-009, serial number 596).

Post-Meeting Note:



**APPEARS THIS WAY
ON ORIGINAL**

MEETING MINUTES

MEETING DATE: January 26, 2001 **TIME:** 10:30 a.m.-12 noon **LOCATION:** CORPS S300

NDA #: 20-998/S-009

Meeting Request Submission Date: November 16, 2000

Briefing Document Submission Date: December 21, 2000

DRUG: Celebrex (celecoxib)

APPLICANT: G.D. Searle

TYPE of MEETING: Guidance

FDA PARTICIPANTS:

Robert Delap, M.D., Ph.D.

Jonca Bull, M.D.

James Witter, Ph.D., M.D.

Lawrence Goldkind, M.D.

Sue-Chih Lee, Ph.D.

Dennis Bashaw, Pharm.D.

Laura Lu, Ph.D.

Stan Lin, Ph.D.

Yoon Kong, Pharm.D.

Office Director, Office of Drug Evaluation V

Acting Division Director

Medical Reviewer

Clinical Team Leader

Pharmacokinetics Reviewer

Pharmacokinetics Team Leader

Statistics Reviewer

Statistics Team Leader

Project Manager

INDUSTRY PARTICIPANTS:

Searle/Pharmacia

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Vice-President, Arthritis Clinical Research

Director, Senior Scientific Advisor

Biopharmaceutics

Senior Director, Arthritis Clinical Research

Director, Biostatistics

Senior Vice-President, Global Regulatory Affairs

Senior Director, Arthritis Clinical Research

Director, Biostatistics

Senior Director, Regulatory Affairs

Associate Director, Regulatory Affairs

Pfizer

S. Cristo

G. Lan, Ph.D.

M. Wahba, M.D.

Director, Regulatory Affairs

Distinguished Scientist Statistics Research

Senior Associate Director, Clinical Development

Consultant

MEETING OBJECTIVES: To discuss the best way to present information in a congruous and harmonious for the February 7, 2001, Arthritis Advisory Committee meeting.

DISCUSSION: FDA pointed out to the sponsor that they should, prior to giving their presentation, comment that their data (e.g., forms of graphs, charts, etc.) consists of duration for less than 1-year.

After reviewing sponsor's draft slides, FDA provided comments to help reduce redundancy and better facilitate presentation of information for Arthritis Advisory Committee.

Slide 4- Endoscopic Prevalence of NSAID-induced Gastrointestinal Ulcers

- Please provide additional comprehensive reviews, rather than demonstrating data from a single study.

Slide 5- Incidence of NSAID-Related Ulcer Complications

- Please explain derivation of the data percentages/numbers.
- Please explain how these rates were annualized from short-term dates.

Slides 2 and 8- Mechanism of Action: Celebrex

- Please describe or expand upon COX-1 and COX-2 roles' in endothelial cells and platelet-endothelial interaction.

Slide 12- Incidence of Ulcer Complications (Data from ~ 13,000 patients NDA submission)

- Please clarify mean exposures in incidence of ulcers.
- Please use a consistent measurement of rates (e.g., annualized vs. crude).
- Please address specifically what type of rate used in all your slides.

Slide 16- CLASS Trial

- Please discuss and explain your rationale for use of OTCs and prescription-NSAIDs in CLASS trials.

Slide 18- Primary Endpoint: UGI Ulcer Complications

- Please clarify/explain your definitions and categories for UGI ulcer complications (e.g., bleeding, perforation, obstruction) under the rubric of nomenclature; thus, the same lexicon would be used and understood.

FDA emphasized the need to explain the data generated and the new knowledge acquired from the CLASS trial as they relate to the standard language present in the current GI template. FDA reminded sponsor that this lexicon would be important for understanding of issues disciplines, other than clinical.

- Please explain endpoints in detail in CLASS trial (e.g., CSUGIEs- ulcer complication: symptomatic vs. ulcers with definition of complicated ulcers).

Slide 21 - Demographics

Slide 22- Baseline Risk Factors

- Please clarify "n" numbers (e.g., slide 21- Demographics - *Celecoxib n=3987* vs. slide 22- Baseline Risk Factors *Celecoxib n =3995*).
-

Sponsor indicated that this was a simple error and would be rectified.

Slide 23- CLASS Data (GI Outcomes and General Safety)

- Please clarify whether ulcer complications are defined by CSUGIEs and GDUs.

Slide 24- Ulcer Complication and Symptomatic Ulcer Rate- All Patients

- Please address the use of annualized incidence rates.

Slide 31-

FDA suggested that the sponsor distinguish different comparators to illustrate any detectable differences and how these differences relate to the data contained in the current celecoxib labeling. Further, with respect to statistics, FDA suggested that results of all three-treatment arms should be shown.

Sponsor noted this and stated that they would incorporate FDA's comments.

Sponsor request clarification on the NSAID claim. Sponsor indicated that they would not make the claim that celecoxib was in the same class of NSAIDs because they understand that any class claim would need to meet all criteria for that specific drug class. Sponsor noted that celecoxib showed a difference in GI toxicity vs. ibuprofen.

Slide 34- Comparisons with Individual NSAIDs

- Please clarify the type of rate of incidence (e.g., annualized or crude).

Slide 35- Underestimation of GI Events Due to GI Intolerance

- Please note that there is substantive disagreement with respect to this slide.
- Please justify the inclusion of diarrhea in GI intolerance.

Following FDA comments on sponsor's draft slides, sponsor presented update slides that were not submitted to the FDA prior to this meeting.

In essence, sponsor agreed that the primary endpoint was not successful for CLASS trial; no statistical significance. However, sponsor states that the results do provide important information, which speaks to GI safety with respect to celecoxib vs. ibuprofen. Also, sponsor notes that the analysis of CSUGIEs and GDUs combined is clinically meaningful.

Given the fact that primary endpoints did not prove to be statistically significant, sponsor indicated that they would provide nominal p-values. The sponsor expressed that one of the most important questions to be answered is "what does statistical significance mean in the face of clinical data?"

Combined Analysis (CSUGIEs and GDUs- not pre-specified endpoints)

Sponsor requested two points of clarification regarding FDA's draft slides for the Arthritis Advisory Committee Meeting.

Sponsor indicated that the FDA cited that certain analysis as being "*post-hoc*". Sponsor wanted to clarify that these analyses were actually pre-specified. Sponsor noted that they identified symptomatic ulcers as an endpoint defined in advance in the protocol.

FDA asked if the CSUGIEs and GDUs were combined in the analysis. Sponsor responded that symptomatic ulcers and GDUs were combined as defined in the protocol, but how the analysis was conducted was not described *a priori*.

Sponsor noted that according to disease definition, an ulcer complication would be categorized as having a defined lesion via an endoscopy, in addition to fulfilling other set stringent criteria.

FDA asked the sponsor if they were going to emphasize ulcer complications during their presentation for the Arthritis Advisory Committee Meeting. Sponsor responded that they would focus on the combination analysis of CSUGIEs and GDUs to present information on safety of celecoxib.

Sponsor noted that the combined analysis of symptomatic ulcers and ulcer complications using diclofenac and ibuprofen as comparators. According to sponsor, a statistical difference was observed with ibuprofen.

FDA asked if something would be lost by sponsor's proposed combined endpoint analysis of CSUGIEs and GDUs. FDA further pointed out that considering the pre-specified endpoints were

not met in this trial (mutually agreed upon by sponsor), it is necessary to properly explain the purpose of the protocol endpoints.

FDA reminded the sponsor that they should not lose the importance of how the definitions of CSUGIEs and GDUs were crafted and recommended that sponsor utilize the current label of celecoxib for historical background of GI toxicity.

Informative Censoring

FDA stated that it would important to include aspirin data as part of this GI outcome study. Sponsor agreed that important information extracted from the data generated for GI outcomes on non-aspirin users. In spite of this, the sponsor noted that it would not be prudent to conclude that celecoxib and aspirin showed any difference since this trial was not designed to illustrate this point.

FDA asked if the sponsor intended to present information on aspirin use and non-use in this trial. Sponsor replied that they would present if an issue was raised, however, they did not plan to present.

FDA noted that aspirin as a risk factor in this trial reflects globally cardiovascular issues. Sponsor indicated that they were not prepared to present this aspect during their presentation, however, they would address issues if they would arise during the meeting.

FDA suggested that the sponsor could present the aspirin information, then could focus on non-aspirin users for GI outcomes data followed by examining other endpoints associated with non-aspirin users. Sponsor agreed.

FDA reminded the sponsor that the overall purpose would be to disseminate valuable information for aspirin use in GI and other organ systems for safety data collection. Further, FDA noted that safety datasets in both aspirin and non-aspirin users would provide useful information beyond the scope of the Advisory Committee meeting.

FDA requested that the sponsor re-examine the dataset for combined analysis from a statistical perspective (e.g., without the censoring rule, statistical results were consistent with sponsor's report, however, with censoring rule, statistical results were not consistent). Time to CSUGIEs vs. time to combined events - inconsistencies were noted.

FDA touched upon the issue of informative censoring in this trial. FDA stated that informative censoring would be important in all types of trials, hence some discussion on this issue would be useful as part of the presentation for the Advisory Committee meeting. Sponsor stated that informative censoring would inject bias into the study and could affect the final analysis due to withdrawal to GI symptoms as informative censoring.

FDA emphasized the importance of addressing informative censoring with respect to future conceptual study designs. FDA informed the sponsor that they could keep topic of informative censoring on a larger more global scale rather than directly tying it to the CLASS trial for presentation. Sponsor noted that they could try to summarize informative censoring as a general concept and context of discussion.

Sponsor indicated that they eliminated slides on open-label and post-marketing surveillance. Also, sponsor noted that they modified their slides in their conclusions to reflect changes outlined in the CLASS trial.

FDA stated that OPDRA would be prepared to field questions, but they would not make a formal presentation for the Advisory Committee meeting.

FDA made some suggestions to sponsor in terms of slides. FDA stated that it would be useful to present data more completely by including information for both CLASS and original NDA submission for celecoxib.

Additional Issues

Sponsor asked about the questions for Advisory Meeting. Dr. Delap pointed out that typical questions are global questions for future development. Also, Dr. Delap noted that concerns are that COX-2 inhibitors are fairly widely seen as GI safe drugs, however, there are still risks associated with COX-2s.

Pharmacokinetic

Sponsor presented slides on diclofenac formulation used in blind studies (Voltaren- no longer commercially available).

FDA stated that the original data did not include the full dissolution test on Voltaren tablets (enteric coated and delayed-release). Sponsor noted that Voltaren - T_{max} occurred later while diclofenac formulation- T_{max} occurred earlier; there was no release of diclofenac in an acidic medium).

FDA requested that further explanation would be needed for why diclofenac tablets dissolve slower in a neutral pH, but show a shorter T_{max}. Sponsor responded that the *in vitro* dissolution solution used in the Pharmacopoeia for the standard Voltaren tablets are highly variable with regard to plasma concentration.

Sponsor stated that the enteric formulation is highly variable because peak values depend on gastric emptying time.

FDA asked the sponsor to discuss the COX-2 hypothesis in terms of plausibility to current science and medicine. FDA reminded the sponsor that as always, we would need confidence in the data results and scientific evidence presented in a study to determine the content of the labeling for a drug product.

ACTION ITEMS:

1. FDA will continue to communicate with sponsor regarding any issues for clarification in preparation for the Arthritis Advisory Committee Meeting.
 2. FDA will convey minutes to sponsor.
-

Yoon Kong, Pharm.D.
Project Manager

Concur: _____
Jonca C. Bull, M.D.
Acting Division Director

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Jonca Bull

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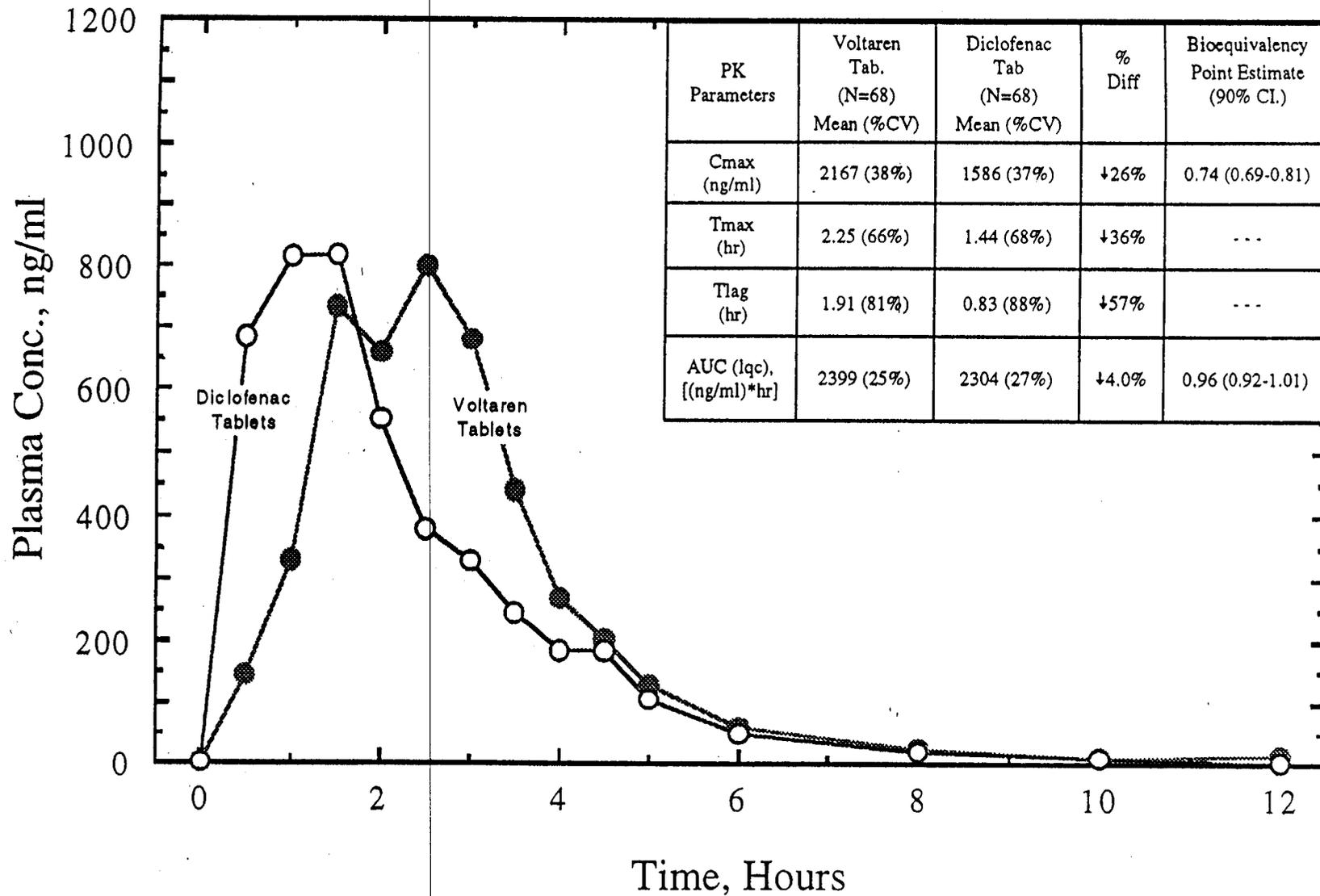
CLASS

- Primary endpoint was not significant
 - ASA
 - Hypervigilance
 - Changed medical practice
- Results provided important information
- Analysis of CSUGIEs/GDU combined is clinically meaningful
 - GDUs require medical intervention

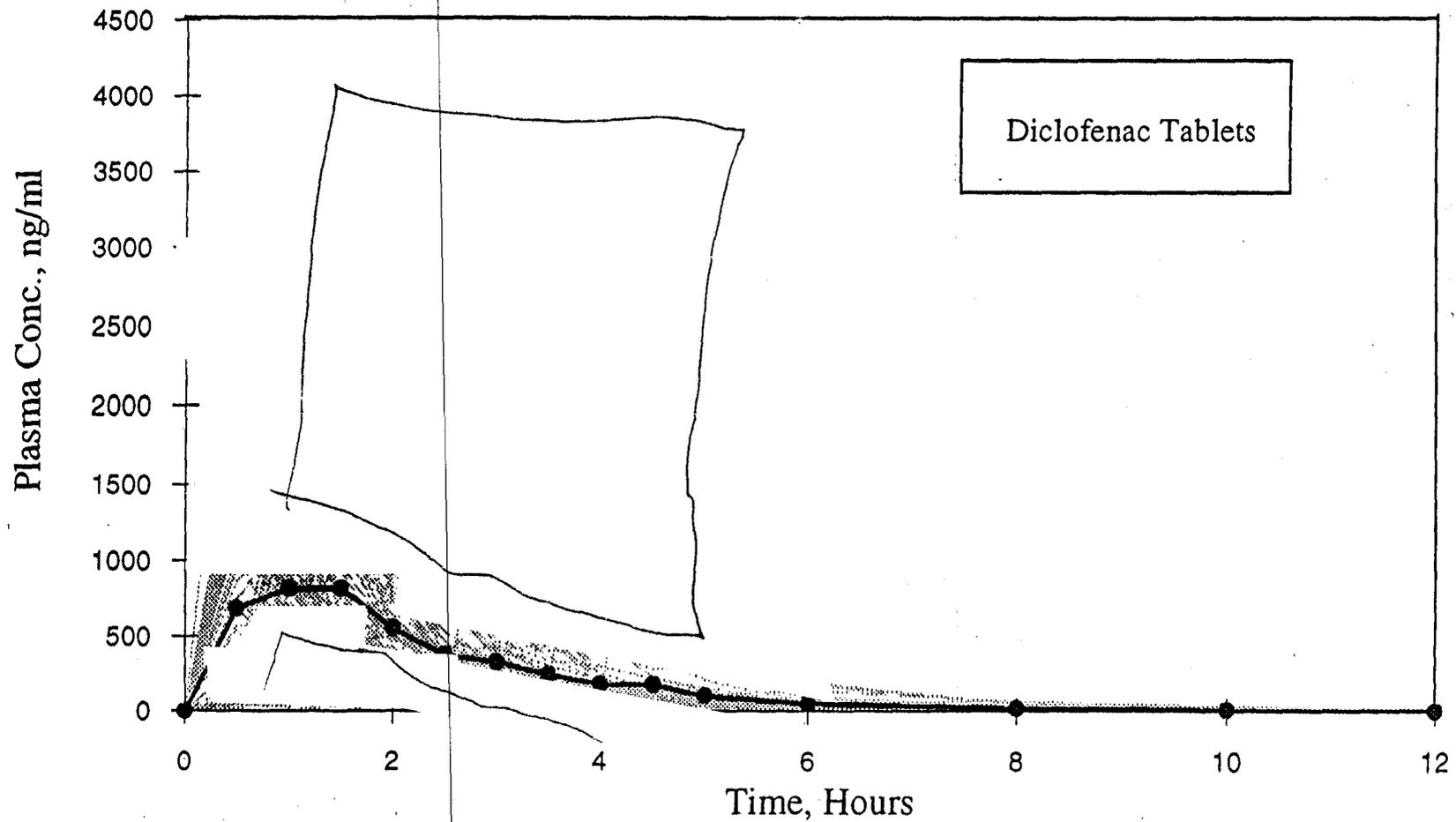
CLASS

- Will use entire study results for presentation
- Will replace 6 months analysis and imputation with the analysis of CSUGIEs/GDU combined
- Non-ASA analyses

Mean diclofenac plasma concentrations (mean of initial and repeat values; N = 68 Observations) in 35 subjects following single 75 mg dose given as diclofenac tablets (○) or Voltaren commercial tablets (●) in a replicate designed bioequivalency study



Individual (.....) and mean (●) diclofenac plasma concentrations (initial and repeat values; N = 68) in 35 subjects following single 75 mg dose given as diclofenac tablets in a replicate designed bioequivalency study



Comparative Bioavailability: Voltaren vs Diclofenac Tablets

Conclusions

- ① Diclofenac tablets were bioequivalent to the commercial Voltaren tablets for total diclofenac exposure (AUC) in plasma
- ② If diclofenac safety is related to the total drug exposure, then diclofenac tablets and Voltaren tablets should exhibit similar safety profile
- ③ Diclofenac C_{max} values with the diclofenac tablets were lower ($\downarrow 26\%$) than Voltaren tablets
- ④ If diclofenac safety is related to peak drug exposure (C_{max}) then diclofenac tablets would under estimate the safety of Voltaren tablets

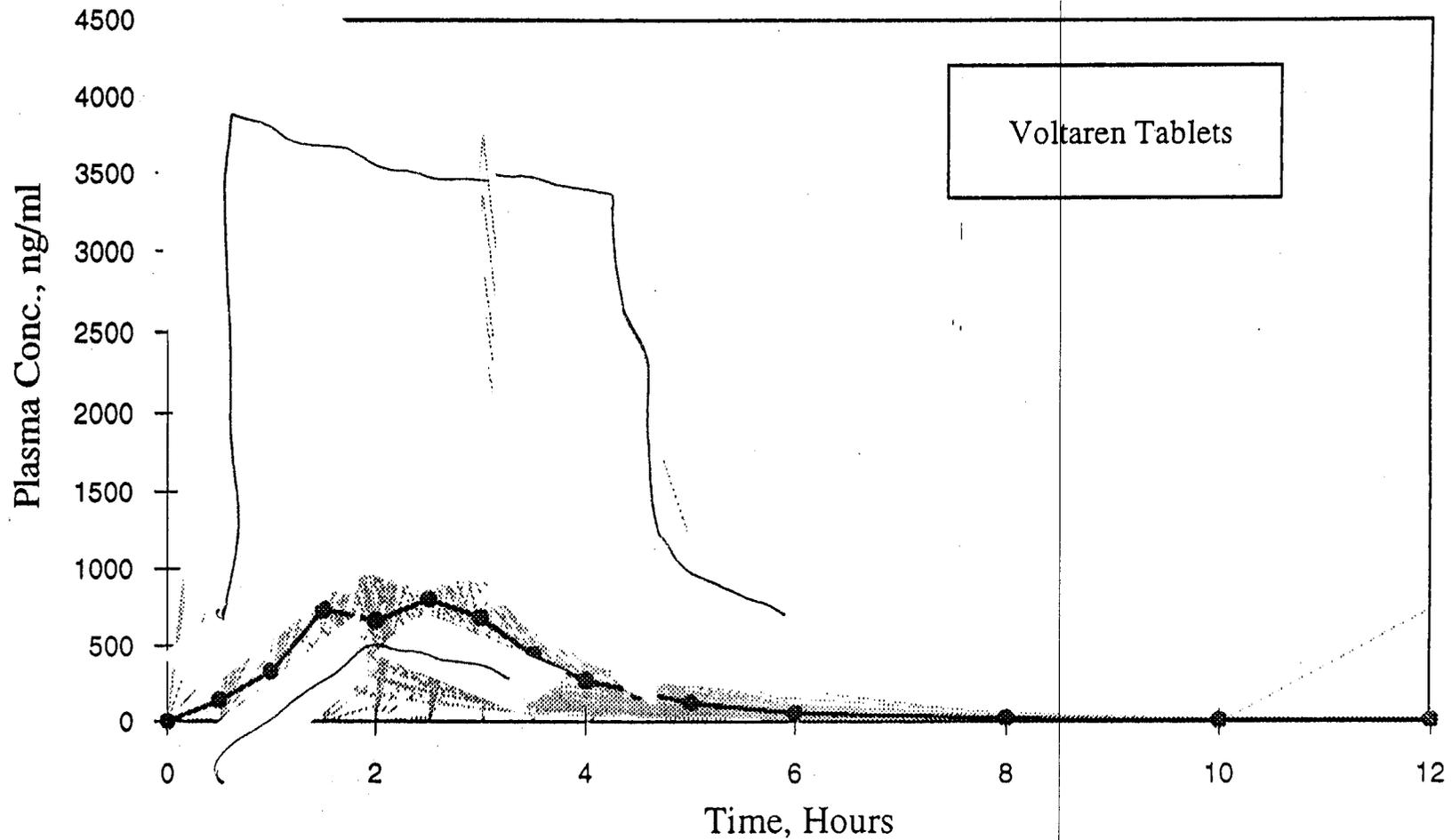
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Clinical Pharmacology/Biopharmaceutics Review

FDA Synopsis

- ① In the CLASS 2 trial, a formulation of diclofenac sodium comprised of a 75 mg enteric-coated diclofenac sodium was used in lieu of the marketed Voltaren tablets to achieve the desired blinding
- ② Mean diclofenac AUC was within 80-125% range but mean C_{max} was lower and mean T_{max} was shorter compared to Voltaren tablets
- ③ The sponsor considers this lack of bioequivalency in diclofenac C_{max} not clinically important. We disagree with the sponsor in this regard since there is no scientific evidence to rule out diclofenac C_{max} as an important parameter related to safety
- ④ Therefore, the safety profile of Voltaren tablets may be worse than what was for diclofenac tablets in the CLASS 2 trial

Individual (-----) and mean (●) diclofenac plasma concentrations (initial and repeat values; N = 68) in 35 subjects following single 75 mg dose given as Voltaren tablets in a replicate designed bioequivalency study



TELECON MINUTES

Meeting Date: October 26, 1999

Time: 2:15 – 3:30 p.m.

NDA 20-998

Drug: Celebrex (celecoxib)

Sponsor: Searle

Type of meeting: Clinical Guidance

Attendees:

FDA

Lawrence Goldkind, M.D.
 Medical Officer (DGCDP)
 John E. Hyde, Ph.D., M.D.
 Deputy Division Director
 Stan Lin, Ph.D., Statistics Team Leader
 Constance Lewin, M.D., Project Manager
 Karen Midthun, M.D.
 Acting Division Director
 James Witter, M.D., Ph.D., Medical Officer

Sponsor

Searle:

A. Burr
 D. Jordan
 J. Kent
 J. Lefkowitz
 C. Maurath
 W. Begley

Pfizer:

P. Christesen
 J. Finman
 E. Forster
 W. Frost
 L. Loose
 M. Wahba

Meeting Chair: Karen Midthun, M.D.

Meeting Recorder: Constance Lewin, M.D.

Meeting Objective:

This teleconference was requested by sponsor to discuss items related to event censoring, study termination, data analysis and sNDA preparation for the CLASS studies. Specific items for discussion were provided in correspondence dated October 11, 1999 (Serial number 444).

Discussion Points:

- **Event censoring**

Participants agreed that sponsor's proposal was representative of earlier discussions with the Division. The Division conveyed its concerns about the overall safety perspective, especially as it pertains to anaphylactoid events and sulfa reactions. The Division pointed out that