CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-776

STATISTICAL REVIEW(S)

9 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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Statistical Review and Evaluation

NDA: 20-776

Drug Name: — (oxaprozin potassium 600mg caplets)

Applicant: G.D. Searle & Co.

Statistical Reviewer: Richard A. Stein Review #1, Date: November 25, 1997

Correspondence Date: 5/19/97 FDA Stamp Date: 5/20/97

Reviewing Medical Officer: Christina Fang, MD

Volumes Reviewed: 1.1, 1.2, 1.52, 1.54, 1.56, 1.58, 1.60, 1.62

Indications: Relief of — symptoms of rheumatoid and osteoarthritis.

I. Summary Findings and Background Information

Searle has submitted studies 007,009, 010, 016 as —

— is a salt of Daypro (oxaprozin acid) having greater water solubility than Daypro. Daypro is an approved nonsteroidal anti-inflammatory prescription drug made by Searle for the management of signs and symptoms of rheumatoid arthritis and osteoarthritis. Because of slow onset, Daypro is not indicated for acute pain. Searle is seeking approval for once-a-day — labeling for the — symptoms of rheumatoid and osteoarthritis. Because of its faster dissolution, — is postulated to have faster clinical onset of analgesic action than Daypro while retaining once-a-day dosing capability. The sponsor states that oxaprozin potassium 1356 mg is equivalent to 1200 mg oxaprozin acid. Thus, Searle refers to oxaprozin potassium 1356 mg as "oxaprozin potassium 1200 mg".

— four postsurgical dental pain studies to be —

— Eleven clinical efficacy studies with investigator name within parentheses are under consideration: N48-95-02-004 (— N48-95-02-007 (N48-96-02-009 — N48-96-02-010 — N48-96-02-016 — ; N48-94-02-001 (— N48-95-02-005 (Anderson), N48-95-02-006 (30 investigators). N48-95-02-008 (— , N48-95-02-012 — and N48-95-02-013 — . Of these 11 studies, only the first 5 are placebo controlled in addition to being randomized and at least single blind. Of these 5 placebo controlled acute dental pain trials, the sponsor considers N48-95-02-007 — , N48-96-02-009 — , N48-96-02-010 — , N48-96-02-016 (—

Study N48-95-02-006 was a 24 week parallel group, placebo controlled, multicenter efficacy study in patients with moderate to severe osteoarthritis (OA) of the knee.

II. Study Characteristics

Each of the 4 — clinical trials (N48-95-02-007, -009, -010, -016) was a randomized, placebo controlled, double blind, parallel group study in the acute dental pain model, having approximately 50 patients per treatment arm. Study 007 lasted 24 hours, studies 009 and 010 lasted 12 hours, and study 016 lasted 8 hours.

Study N48-95-02-004 was a randomized, single blind, placebo controlled, acute dental pain trial with three treatment groups: oxaprozin potassium, oxaprozin acid, and a mixture of these forms of oxaprozin.

Study N48-95-02-006 was a 24 week placebo controlled, parallel group, randomized, double blind 28-investigator/30-site efficacy study in 803 patients having moderate to severe osteoarthritis (OA) of the knee. Treatment groups studied were Xopane 1200mg, Oxaprozin acid 1200mg and placebo. Primary efficacy variables included Patient and Physician Evaluation, Pain on Motion, and Pain on Weight Bearing.

III. Sponsor's Statistical Analyses and Results

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

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B. Osteoarthritis

The sponsor stated their analyses show [redacted] be effective in patients with moderate to severe osteoarthritis (Vol. 1.62, pages 029-031). Based on the analyses provided by the sponsor, this is essentially correct. The reader not interested in the details of how I come to the same conclusion as the sponsor's should skip forward to section IV.

The sponsor's analyses were performed by carrying last observation forward. An analysis of covariance model was used to analyze the data with treatment and center as factors and baseline as a covariate. Mean changes from baseline for [redacted] 1200mg for the Patient's Global Assessment, Physician's Global Assessment of osteoarthritis, Knee Pain on Weight Bearing, and Knee Pain on Motion were reported to be statistically significantly greater than placebo at all visits (weeks 2, 6, 12, and 24).

Using Q-statistic methodology, the sponsor also showed for all four of the efficacy variables above that in the comparison of [redacted] to Oxaprozin Acid: $0.8< Q<1.2$ and $0.6< Q_L$. Consistent with statistical reviews of osteoarthritic drugs that have been done in the past, one could conclude that [redacted] comparable in effectiveness with Oxaprozin Acid. These statistical procedures are currently considered acceptable by this reviewer.

My interpretation of their analyses is that some the sponsor's conclusions above are not entirely consistent with the analytical results they presented; but the overall impact of this is nevertheless considered negligible. First, the dropout rate at week 24 (Vol. 1.62, page 059-060) is too high to have confidence in statistical results, particularly when making comparisons to placebo.

Table 3: Dropout Rates in Osteoarthritis

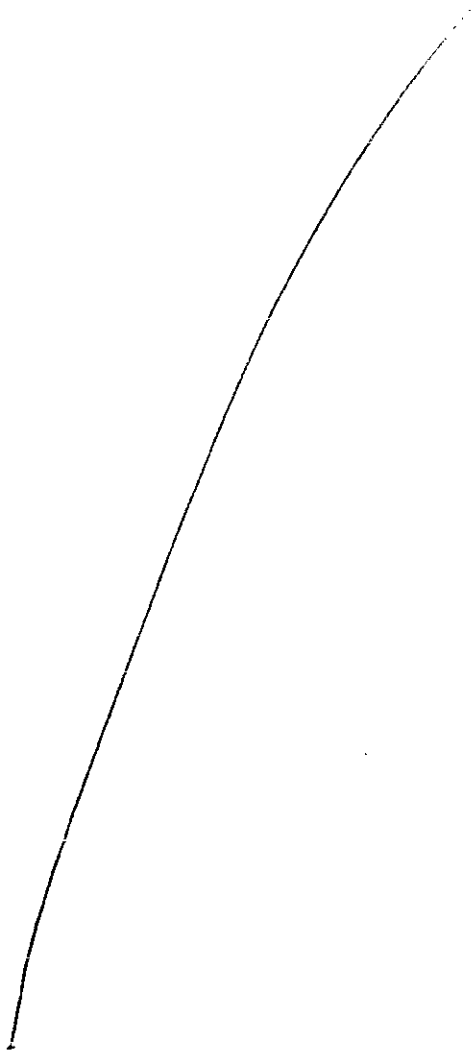
% Dropout	Baseline	Week 2	Week 6	Week 12	Week 24
Placebo	0%	19%	37%	44%	50%
Oxaprozin	0%	10%	23%	33%	41%
[redacted]	0%	13%	28%	34%	40%

Second, when Fisher's protected LSD procedure is applied to the Patient's Global Evaluation (Vol. 1.62, page 072), it appears that at week 24, the overall test for treatment effect barely fails to be significant at $p\leq 0.05$, i.e., $p=0.068$.

Conclusions based on the sponsor's results alone could take the following logical order. There is early evidence (week 2 and possibly week 6) from this trial that oxaprozin acid is effective. Thus this trial does not seem to be a failed study. Given that oxaprozin acid is an approved drug having rather slow onset of action, it is plausible that the early effectiveness of oxaprozin acid

is maintained at weeks 12 and 24. With this in mind, note that — is effective at week 2 based on the comparison of Oxaprozin to placebo and is comparable in efficacy to a drug believed to be effective, Oxaprozin acid, at weeks 2, 6, 12, and 24 based on the Q-statistic. In this way, the applicant's results lead to inferring the effectiveness of — 1200mg in OA of the knee in this study.

IV. Reviewer's Statistical Analyses and Results



V. Reviewer's Comments

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2.

3.

Richard A. Stein

Richard A. Stein, Ph.D.
Mathematical Statistician

Concur:

M J Huque 12/2/97

Mohammad Huque, PhD
Acting Director, Div. of Biometrics IV

Archival: NDA 20-776

cc: HFD-550/Christina Fang, MD
HFD-550/Victoria Lutwak, CSO
HFD-550/Div. File
HFD-340/Div. Sci. Inv.
HFD-725/Richard Stein, PhD
HFD-725/Div. File

HFD-725/ Huque

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JUN 30 1997

STATISTICAL REVIEW AND EVALUATION

45/21 DAY MEETING REVIEW

(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

NDA:	20-776
DRUG CLASS:	2S
NAME OF DRUG:	— (Oxaprozin Potassium)
APPLICANT:	G.D. Searle & Co.
SUBMISSION DATE:	19 May 1997

INDICATION(S): 1200 mg — s labeled for —
(2) Signs & symptoms of rheumatoid and osteoarthritis.

NUMBER AND TYPE OF CONTROLLED CLINICAL STUDIES BY INDICATION:
(1) 5 Dental pain studies, (2) 1 OA study.

STATISTICAL REVIEWER:	Richard Stein
CLINICAL REVIEWER:	Christina Fang
PROJECT MANAGER:	Chin Koerner

45 DAY MEETING DATE:	23 June 1997
WAS THE NDA FILED:	yes
IF YES, DUE DATE :	21 September 1997
USER FEE DATE:	19 May 1998

I. ORGANIZATION AND DATA PRESENTATION

		YES	NO	N/A
A.	Is there a comprehensive table of contents with adequate indexing and pagination?	X		
B.	Are the original protocols, protocol amendments and proposed labels provided?	X		
C.	Adverse event listings by center and time of occurrence relative to enrollment date.	X		
D.	Is a CANDAR or an electronic submission of the data necessary?		X	
E.	If the data have been submitted electronically, has adequate documentation of the data sets been provided?	X		
F.	Are inclusion/exclusion (evaluability) criteria adequately coded and described:	X		
G.	Are there discrepancies between CRF information and CANDAR/Jacket data?			X
H.	If the data have been submitted electronically, can laboratory data be easily merged across studies and indications?			X

II. STATISTICAL METHODOLOGY

		YES	NO	N/A
A.	Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?	X		
B.	For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable sub populations (age, gender, race/ethnicity, etc.)?	X	X*	
1.	If subset analyses were not done, was an acceptable explanation of why given?		X	
C.	Based on the summary analyses of each study, do you believe:	////	////	////
1.	The analyses are appropriate for the type data collected, the study design, and the study objectives (based on protocol and proposed label claims)?	X		
2.	If there are multiple endpts, has this been adequately addressed?	X		
3.	Intent-to-treat (ITT and MITT) analyses are properly performed?	X		
4.	Sufficient and appropriate references were included for novel statistical approaches?			X
D.	If interim analyses were performed, were they planned in the pro -tocol and were appropriate significance level adjustments made?			X
E.	Are there studies which are incomplete or ongoing?	X		
F.	Is there anything significant yet regarding safety or AE evaluations?		X	

III. FILEABILITY CONCLUSIONS

There are ongoing studies are for migraine, low back pain, and OA of the knee. These studies are not critical for the present indication sought. At this point, I have found no efficacy analyses that account for sex, age, and race*. I have found no data for single-blind study 004.

From a statistical perspective, this submission is reviewable with only minor further input from the sponsor. However, at face value, the results for —

Richard A. Stein

Richard A. Stein
Biomedical Statistician, PhD, DOB IV

Hoi M. Leung

Concur: Hoi M. Leung, Ph.D.
TEAM LEADER
Biomedical Statistician, DOB IV

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HFD-550/RMO/Dr. Fang
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