CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-776

ADMINISTRATIVE DOCUMENTS

PATENT STATEMENT UNDER 21 USC 355(B)(1)

The applicant declares that there are no relevant issued U.S. Patents claiming the drug, any formulation of the drug nor any methods of use of the drug which drug oxaprozin potassium is the subject of this application and which could reasonably be asserted by G.D Searle & Co., who is also the present NDA applicant if a person not licensed by G. D. Searle & Co. engaged in the manufacture, use, or sale of the drug product.

EXCLUSIVITY SUMMARY for NDA # 20-776 SUPPL #

Trade Name Daypro ALTA **Generic Name** Oxaprozin
Applicant Name G.D. Searle
HFD- 550
Approval Date October 17, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X__/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /__X_/ NO /___/

If yes, NDA # 18-841 Drug Name Daypro

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Nancy M. Halonen
Signature of Preparer
Title: Project Manager

October 17, 2002
Date

Lee S. Simon, M.D.
Signature of Office or Division Director

October17,2002
Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lee Simon
11/25/02 06:43:36 PM

(Complete for all original applications and all efficacy supplements)

NDA/~~PLA~~ # 20-776 Supplement # — Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 550 Trade (generic) name/dosage form: Benilas (oxaprozin potassium) Action: AP AE NA

Applicant G.D. Searle Therapeutic Class 25

Indication(s) previously approved Osteoarthritis and Rheumatoid Arthritis
Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Proposed acute pain & OA & RA
(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing.
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
✓ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Carmen DeBellas — 9/30/97
Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/~~PLA~~ # 20-776
HFD 550 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

'95

DEBARMENT CERTIFICATION

Pursuant to section 306(k) of the Federal Food, Drug and Cosmetic Act, the applicant did not employ or otherwise use in any capacity the services of any person debarred under subsection (a) or (b), in connection with this application.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 20-776	Efficacy Supplement Type SE-	Supplement Number	
Drug: Daypro ALTA		Applicant: G.D. Searle	
RPM: Nancy Halonen		HFD-550	Phone # 827-2090
Application Type: (x) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	( ) Standard (x) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	October 18, 2002
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(x) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(x) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(x) Verified 19 Jun 1996
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	17Oct.2002
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	17 Oct. 2002

General Information	
❖ Actions	
• Proposed action	(x) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(x) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(x) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (x) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	10/11/02
• Original applicant-proposed labeling	3/21/97
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	M.O. reviews: 10/15/02, 5/20/97 OPDRA: 8/14/02, 12/3/01, 7/7/00 DDMAC: 12/17/01
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	See enclosed
❖ Memoranda and Telecons	Se enclosed
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	6/23/97
• Pre-NDA meeting (indicate date)	6/27/97
• Pre-Approval Safety Conference (indicate date; approvals only)	5/20/98
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	none
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/a

MEMORANDUM OF TELECON

DATE: September 23, 2002

APPLICATION NUMBERS: NDA 20-776 (Daypro ALTA)

BETWEEN:

Name: Sue Tegtmeyer Manager, Global regulatory Affairs.
Winifred Begley Regulatory Affairs
Marcia Shafski Labeling

Representing: Pharmacia Corporation

AND

Name: Dr. James Witter Medical Team Leader
Dr. Christina Fang, Medical Reveiwer
Carmen DeBellas Chief Project Manager
Nancy Halonen Project Manager

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

SUBJECT: Reach concurrence on Final Draft Label for Daypro ALTA.

- Both the Sponsor and the Division agreed that the use of [redacted] to distinguish adverse events associated with oxaprozin /oxaprozin potassium from those reported with the use of other NSAIDs is confusing.

- The Sponsor proposed to remove all the [redacted] throughout the Daypro Alta label as well as the Daypro label to maintain consistency in labeling, and the Division accepted.

- The Sponsor agreed to delete the Adverse Events that are listed twice in the less than 1 percent category and will retain the Adverse Events listings of 1 to 10 percent to simplify the text.

- The Sponsor will send copies of the Final Draft Label in Word format electronically and in hard copy for final review.

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

Medical Team Leader, HFD-550

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: June 21, 2002	**DUE DATE:** August 21, 2002	**ODS CONSULT #:** 00-0129-2

TO: Lee Simon, M.D.
Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

THROUGH: Nancy Halonen
Project Manager
HFD-550

PRODUCT NAME: Daypro ALTA (Oxaprozin Potassium Tablets) 600 mg **NDA #:** 20-776	**NDA SPONSOR:** Pharmacia

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Anti-Inflammatory, Analgesics, and Ophthalmologic Drug Products (HFD-550), the Division of Medication Errors and Technical Support (DMETS) has conducted a review of the proposed proprietary name "Daypro ALTA" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS has no objections to use of the proprietary name "Daypro ALTA". In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Phone: (301) 827-3242
Fax: (301) 443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420; Room 15B-32)

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 5, 2002

NDA NUMBER: 20-776

NAME OF DRUG: **Daypro ALTA**
(Oxaprozin Potassium Tablets)
600 mg

NDA SPONSOR: Pharmacia

I. INTRODUCTION

This consult was written in response to a request from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550) for assessment of the proprietary name, *Daypro ALTA*. The container label, unit dose and package insert labeling were reviewed for possible interventions in minimizing medication errors. Additionally, the sponsor submitted an independent analysis of the proposed name that was conducted by — These findings were submitted to DMETS for review and comment as well.

The sponsor, Pharmacia, originally submitted the proposed proprietary names, "Daypro — and "Daypro — DMETS completed a Proprietary Name Review for these names on October 31, 2001. DMETS did not object to the use of the proprietary name Daypro — out did not recommend the use of the proprietary name Daypro — see ODS Consult 00-0129-1). However, the sponsor requests to change the proprietary name from Daypro — to Daypro ALTA.

The sponsor, Pharmacia, currently markets Daypro in the following strength and dosage form:

Daypro (Oxaprozin Tablets: 600 mg)

PRODUCT INFORMATION

Daypro ALTA contains the active ingredient oxaprozin potassium, which is a member of the propionic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Daypro ALTA is indicated for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis. The recommended dose for Daypro ALTA is 1,200 mg by mouth once daily. Daypro ALTA will be available as 600 mg oral capsule-shaped tablets.

II. RISK ASSESSMENT

The standard DMETS proprietary name review was not conducted for this consult, because the proprietary name "Daypro" has been utilized in the U.S. marketplace since December 1993. An Expert Panel discussion was conducted to address concerns with the use of the modifier "ALTA". In addition, the Adverse Event Reporting System (AERS) and Drug Quality Reporting System (DQRS) databases were searched to determine if there is any confusion with the use of the proprietary name "Daypro."

A. EXPERT PANEL DISCUSSION

A discussion was held by DMETS to gather professional opinions on the safety of the proprietary name *Daypro ALTA*. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS's Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The panel expressed concerns that the modifier, "ALTA", which represents the salt formulation of Daypro, does not represent anything. However, the panel does not object to the use of a modifier for this proposed product. New "salt" formulations of medications have been introduced to the U.S. market by using either new proprietary names (Cataflam/Voltaren; Naproxen/Anaprox) or by adding modifiers to the already existing proprietary name (e.g., Darvon/Darvon N; Tofranil/Tofranil PM). Consequently, DMETS does not object to the use of a modifier for this proposed product. Lastly, the panel commented that "ALTA" could be confused with "Altace" and "epoetin alfa."

2. DDMAC has no objection to the proposed proprietary name, Daypro ALTA with regards to promotional claims.

B. AERS/DQRS DATABASE SEARCH

DMETS searched *the FDA Adverse Event Reporting System (AERS)* database in order to determine any post-marketing safety reports of medication errors associated with Daypro. The Meddra Preferred Term (PT), "Medication Error," and the drug names, "Daypro%" and "oxaprozin%" were used to perform the search. The *Drug Quality Reporting System (DQRS)* database was also searched for medication error reports with the search terms, "Daypro%" and "oxaprozin%."

A total of 10 reports from the AERS search were retrieved and reviewed. Of the 10 reports reviewed, no account involved name confusion with Daypro.

C. STUDY SUBMITTED BY APPLICANT

Pharmacia requested [redacted] "to assess the suitability of the proposed proprietary name Daypro ALTA." [redacted] study included forty-seven (47) pharmacists from different practice sites, such as hospital and community pharmacies. The respondents were asked to provide answers to six questions: two questions regarding look-alike and/or sound-alike potential of the proposed suffix attached to the trademark Daypro, two questions regarding confusion related to the suffix alone, and two questions regarding suitability of the proposed suffix for the product. As part of the survey, respondents reviewed six hand-writing examples of the suffix attached to the trademark of Daypro. They were also given typewritten samples of the trademark with the suffix attached to it and asked to pronounce the suffix for the product.

[redacted] provided the following conclusion in regard to the proposed name, Daypro ALTA:

> [redacted] found no significant safety risks associated with the proposed name Daypro ALTA. Specifically, [redacted] concluded that the proposed proprietary name was suitable because it is sufficiently distinct from other abbreviations as well as other marketed products with suffixes. While several of the reviewers noted potential interpretations of the "ALTA" suffix, [redacted] concluded that the interpretations would not interfere with the safe use of the product. Additionally, there was a passing similarity to the phrase "Dispense Altace" noted. Upon further consideration [redacted] concluded that the non-name attributes, such as dosage, strengths, minimized the potential for medication errors."

No details of the methodology was given, no information on the criteria used to determine whether or not the situation was a low, moderate, or high risk of confusion, no indication of who determined the levels of confusion and how those levels were determined, and no validation of method was indicated. Therefore, the evaluation lacks pertinent information and cannot be accurately evaluated by DMETS. However, in evaluating the second [redacted] nalysis, DMETS has the following comments:

> We agree with the conclusion provided by [redacted] that the suffix "ALTA" should not pose a significant safety risk although "Daypro ALTA" may look similar to the phrase "Dispense Alatace." Although both Daypro ALTA and Altace are dosed once daily, they do not share overlapping strengths. Daypro ALTA is available as 600 mg tablets and Altace is available as 1.25 mg, 2.5 mg, 5 mg, and 10 mg tablets. Given this difference, the risk of confusion between Daypro ALTA and Altace is minimal.

D. SAFETY EVALUATOR RISK ASSESSMENT

To date, the Agency has no medication error report involving name confusion with Daypro. Therefore, there is insufficient evidence at this time to conclude that the proprietary name, Daypro, has significant potential for name confusion. DMETS will continue to monitor post-marketing medication errors in association with the proprietary name, Daypro.

Daypro ALTA and Daypro share similarities and differences (see Table 1). First, Daypro contains the same active ingredient oxaprozin as the currently marketed Daypro Tablets. However, Daypro ALTA will be available as the salt formulation: oxaprozin potassium tablets. Additionally, both products will be used by the same patient population and prescribed by the same types of prescribers. They will likely be stored next to each other on pharmacy shelves. The only differences between Daypro and Daypro ALTA are the salt formulation, the NDC number and the maximum daily dose.

Table 1. The table below includes characteristics of Daypro ALTA compared to those of the original formulation of Daypro.

Product Name	Daypro ALTA	Daypro
Generic name	oxaprozin potassium	oxaprozin
Dosage form(s)	600 mg tablets	600 mg tablets
NDC #		0025-1381-31 0025-1381-51 0025-1381-34
Usual adult dose*	1200 mg (two 600 mg caplets) PO once daily Maximum daily dose is 1200 mg	OA: 600-1200 mg once daily RA: 1200 mg once daily Maximum daily dose: 1800 mg/day or 26 mg/kg (whichever is lower) in divided doses
Indication	Symptoms of osteoarthritis and rheumatoid arthritis	Symptoms of osteoarthritis and rheumatoid arthritis

New "salt" formulations of medications have been introduced to the U.S. market by using either new proprietary names (Cataflam/Voltaren; Naproxen/Anaprox) ~~or~~ by adding modifiers to the already existing proprietary name (e.g., Darvon/Darvon N; Tofranil/Tofranil PM). Consequently, DMETS does not object to the use of a modifier for this proposed product. In addition, the proprietary name, Daypro, plus a modifier, "ALTA", may decrease the risk of patients taking both formulations in error, resulting in a double dose of the intended medication. For instance, errors have been reported when patients inadvertently have taken both Zyban and Wellbutrin, without realizing they are the same medication.

In reviewing the modifier, ALTA, the expert panel identified Altace and epoetin alfa as possible sound-alike and/or look-alike product names. However, the names, Altace and epoetin alfa, should not pose a problem. Although Daypro ALTA and Altace are dosed once daily, Daypro ALTA and Altace do not share overlapping strengths. Daypro ALTA will be available as 600 mg tablets while Altace is available as 1.25 mg, 2.5 mg, 5 mg, and 10 mg tablets. Epoetin Alfa is an established name for Epogen and Procrit. Daypro ALTA and epoetin alfa share no commonalties except for the similar modifiers "ALTA" and "alfa." Daypro ALTA will be available as tablets (600 mg) while epoetin alfa is available as injections (2000 units/mL, 3000 units/mL, 4000 units/mL, 10,000 units/mL, 20,000 units/mL, and 40,000 units/mL). Given these differences, the risk of confusion between Daypro ALTA and Altace or epoetin alfa is minimal.

We acknowledge that there is a potential risk where "Daypro ALTA" will be inappropriately dispensed instead of "Daypro" and "Daypro ALTA" may be administered instead of "Daypro." Therefore, "Daypro ALTA" may be prone to more than the recommended 1200 mg daily. Consequently, we recommend increasing the prominence of the usual dosage statement, "Take two tablets daily" by placing it on the container label and carton labeling. We also recommend careful monitoring and sufficient education regarding the difference between "Daypro ALTA" and "Daypro" upon the launch of this product.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container label, unit dose and package insert labeling for Daypro ALTA, DMETS has identified several areas of possible improvement, in the interest of minimizing potential user error.

A. GENERAL COMMENTS

The NDC numbers — . This can potentially be a problem because pharmacists may use this to verify the prescription is prepared correctly. Visually it may be difficult to detect an error from the NDC number in this case. Consider differentiating the NDC number by changing the number OR by using **color**, boxing or any other means.

B. PACKAGE INSERT LABELING

We recommend including a precautionary statement that advises against the concomitant use of oxaprozin-containing products such as Daypro.

IV. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Daypro ALTA.

2. DMETS recommends implementation of the labels and labeling as outlined in section IV of this review.

DMETS decision is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, project manager, at 301-827-3242.

_____

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety (ODS)

Concur:

_____

Alina R. Mahmud, RPh.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hye-Joo Kim
8/14/02 01:22:17 PM
PHARMACIST

Alina Mahmud
8/14/02 01:34:01 PM
PHARMACIST

Jerry Phillips
8/14/02 01:40:15 PM
DIRECTOR

15 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

17 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Meeting Minutes

Type of Meeting: Teleconference

Subject: Discussion of the Benilas approvable letter of May 20, 1998

NDA: 20-776

Sponsor: GD Searle

Date: May 28, 2998

Attendees: J Hyde, C Fang, V Lutwak,

Searle: Rich Spivey, Steve Hurley, Tomas Bocanegra, Daryl DeKarske

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Overview/Background: The Benilas approvable letter of May 20, 1998

" There is adequate information to support the proposed osteoarthritis and rheumatoid arthritis indications. However, there is inadequate information to support the — indication for the following reason:

The sponsor wanted clarification or additional information from the Division on the three sentences above.

Clarification

A discussion followed covering the following topics.

Action Item: Send a copy of the medical and statistical review to the sponsor.

cc:

NDA 20-776
DivFile
HFD-550/ J Hyde/ C Fang
HFD-550/ CSO/ V Lutwak

Also, See AE package 5/20/98

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-776 Drug Benilan Applicant Searle

RPM Sharon Schmidt Phone 301-827-2536

☐ 505(b)(1)
☐ 505(b)(2) Reference listed drug _____

☐ Fast Track ☐ Rolling Review Review priority: ☒ S ☐ P

Pivotal IND(s) I 47,340

Application classifications:
Chem Class 25
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary 7/24/00
Sedondary _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

◆ User Fee Information ..... ☐ User Fee Waiver (attach waiver notification letter) ☐ User Fee Exemption

◆ Action Letter ..... ☐ AP ☒ AE ☒ NA

◆ Labeling & Labels
FDA revised labeling and reviews ..... _____
Original proposed labeling (package insert, patient package insert) ..... see AE pkg
Other labeling in class (most recent 3) or class labeling ..... _____
Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☒ No
Immediate container and carton labels 4/19 4-4
Nomenclature review ... OPDRA 7/6/00

◆ Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☐ is not on the AIP
Exception for review (Center Director's memo) ..... NA
OC Clearance for approval ..... NA

◆ Status of advertising (if AP action) .. ☐ Reviewed (for Subpart H- attach review) ☐ Materials requested in AP letter
N/A.

◆ Post-marketing Commitments
Agency request for Phase 4 Commitments ..... N.A see AE pkg
Copy of Applicant's commitments ..... N.A see AE pkg

◆ Was Press Office notified of action (for approval action only)? ..... N.A. ☐ Yes ☐ No
Copy of Press Release or Talk Paper ..... N.A

Continued ⇨

◆ Abuse Liability review(s) ..... NA
Recommendation for scheduling ..... NA

◆ Microbiology (efficacy) review(s) and memoranda ..... N.A.

◆ DSI Audits ..... memo 7/11/00
☐ Clinical studies ☐ bioequivalence studies

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ CMC review(s) and memoranda .....

◆ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N.A

◆ DMF review(s) ..... N.A

◆ Environmental Assessment review/FONSI/Categorical exemption ..... see AE 5/20/98

◆ Micro (validation of sterilization) review(s) and memoranda ..... N.A.

◆ Facilities Inspection (include EES report)
Date completed 3/2000 ..... ☑ Acceptable ☐ Not Acceptable

◆ Methods Validation ..... see AP (did not need) ..... ☐ Completed ☐ Not Completed

---

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ Pharm/Tox review(s) and memoranda ..... NA

◆ Memo from DSI regarding GLP inspection (if any) ..... see AP pbg

◆ Statistical review(s) of carcinogenicity studies .....

◆ CAC/ECAC report .....

Continued ⇨

◆ Patent
Information (505(b)(1)) ..... see AE pkg 5/20/98
Patent Certification (505(b)(2)) ..... see AE pkg
Copy of notification to patent holder (21 CFR 314.50 (i)(4)) ..... see AE

◆ Exclusivity Summary ..... N.A. for N.A

◆ Debarment Statement ..... ✓

◆ Financial Disclosure
No disclosable information ..... ✓
Disclosable information – indicate where review is located .....

◆ Correspondence/Memoranda/Faxes .....

◆ Minutes of Meetings .....
Date of EOP2 Meeting _____
Date of pre NDA Meeting _____
Date of pre-AP Safety Conference _____ see AP package put with Action Letter also 5/20/98

◆ Advisory Committee Meeting ..... N.A.
Date of Meeting _____
Questions considered by the committee X
Minutes or 48-hour alert or pertinent section of transcript X

◆ Federal Register Notices, DESI documents ..... N.A.

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... N.A

◆ Clinical review(s) and memoranda 7/24/00

◆ Safety Update review(s) .....

◆ Pediatric Information ..... see AE package ..... N.A.
☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
Pediatric Page ..... ☒ see AE pkg

◆ Statistical review(s) and memoranda 7/18/00

◆ Biopharmaceutical review(s) and memoranda ..... N.A.

Continued ⇨

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Meeting Minutes

Type of Meeting: Sponsor

Subject: AE Letter May 20, 1998

NDA: 20-776 Benilas (oxaprozin potassium)

Sponsor: GD Searle

Date: June 12, 1998

Attendees:
FDA: M Weintraub, C Fang, Laura Lu, D Bashaw, V Lutwak
Searle: D DeKarske, R Spivey, T Bocanegra, M Kuss, S Talwaker, Allison Katz

---

Overview/Background: See tecleon minutes May 28, 1998

The Benilas approvable letter of May 20, 1998

" There is adequate information to support the proposed osteoarthritis and rheumatoid arthritis indications. However, there is inadequate information to support the —— indication for the following reason:

Comments on the June 4, 1998 letter:

DRAFT

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_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 23 1998

Robert G. Trapp, M.D.
The Arthritis Center
2528 Farragut
Springfield, Illinois 62704

Dear Dr. Trapp:

On March 24 and 25, 1998, Ms. Susan D. Yuscius, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study(protocol #N48-95-02-006) of the investigational drug oxaprozin potassium, performed for G.D. Searls and Company. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From an evaluation of the inspection report and of the documents collected during the inspection, we find that you conducted the study in general compliance with federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Yuscius during the inspection.

Sincerely yours,

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations, HFD-344
Office of Compliance
Center for Drug Evaluation
and Research

CFN:1423046
Field classification:N
Headquarters classification:
__x__1)NAI
_____2)VAI-no response required
_____3)VAI-response requested

If Headquarters classification is different classification, explain why:

cc:
HFA-224
HFD-344
HFD-340 r/f
HFR-CE6520 - Yuscius
HFR-CE650 - Baumgarten
HFD- 550 Review Division Div. Dir./Doc. Rm.: NDA#20-776
CSO - Vickey Lutwak
MO - Christina Fang

r/d:AEl-Hage - 4/17/98 for Carreras

d/t:slk:4/17/98

File #9517
Note to Rev. Div. M.O.

-40 subjects were enrolled at this site.

-9 subjects medical records were reviewed.

-Two instances where protocol required visits were done outside the time frames as stated in the protocol.

-Study site data are acceptable.

Meeting Minutes

Type of Meeting: Team Meeting

NDA: 20-776 (oxaprozin potassium)

Sponsor: Searle

Date: April 17, 1998

Attendees: Christina Fang, Sue Chih Lee, Assad Noory, Charlotte Yaciw, Vickey Lutwak

DRAFT

7-27- sent to doc. RW + attachment

The meeting was held to update the other reviewers before the labeling meeting on April 29, 1998. Because the NDA is due on May 18, 1998, we are, also, preparing for the action letter.

Updates:

PK: The sponsor never submitted an appropriate study model for the PK/PD study. This is not a requirement for the AE letter, since they will not get the [redacted] claim..
For the AE letter, Phase 4 commitments.
[redacted], Assad is not sure. See action items.

Chemistry: No methods validation or paragraph necessary. Methods were validated when Daypro was approved. For the AE letter, remember to request all labeling; this includes the cartons and bottle labels with the new name. If it is ready now, have the sponsor submit draft or in mock-up form the revised labeling as a minor labeling amendment.
Clinical: Christina will have the labeling ready for the meeting on 4/29. Assad will give her the PK part of the label on 4/24.
AE Letter: Will be based on OA an RA only; they will not get analgesic claim.

ACTION ITEMS:
1. Charlotte will give Christina her CD with the labeling.
2. V will get the Daypro AP letter for the Phase 4 commitments.
3. V will start Action Package review.
4. V will do first draft of the AE letter.

Addendum:
Charlotte had a copy of the approval letter and the MO Review for the Phase 4 commitments, which were fulfilled. See Attached.

cc:
NDA
Div. File
HFD-550/ C Fang/C Yaciw/V Lutwak
HFD-880/ S Lee/ A Noory

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_____ § 552(b)(5) Draft Labeling

Trio

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 13, 1997

FROM: Charlotte A. Yaciw, HFD-550/830

TO: NDA 20-776

SUBJECT: Telecon - Information Request

I spoke with Roger Nosal at Searle about the environmental assessment report submitted 10/7/1997. I requested confirmation that the projected production numbers reflected the amounts of drug substance and not the tablet — and if metabolism can be used to lower the EIC to below 1 ppb. If the EIC number stands, Searle needs to send in the toxicology and photodegradation reports referenced in Section 8 of the report.

I also pointed out the typo in the stability commitment (oxparozin instead of oxaprozin).

He will check with his EA department and respond accordingly.

cc:
NDA 20-776
HFD-550/Division File
HFD-550/Chem/Yaciw
HFD-550/PM/Lutwak
Document ID: n20776tc.mem

Printed by Victoria Lutwak

Electronic Mail Message

Date: 12-Nov-1997 02:09pm
From: Charlotte Yaciw
YACIW
Dept: HFD-550 CRP2 N310
Tel No: 301-827-2050 FAX 301-827-2531

Subject:

Vickey,

I just got to the end of the amendment and discovered that Searle sent a full EA report (not the exclusion claim we expected). I think their projections are grossly inflated and they did not factor in any metabolism, however, this is what they sent in so we have to review it. This means a consult to Nancy Sager for an EA review and FONSI. I'm sorry I didn't catch this sooner.

We can use the report from my review copy of the amendment, its about 50 pages. I'll give it to you tomorrow.

Charlotte

Printed by Victoria Lutwak

Electronic Mail Message

Date: 12-Nov-1997 09:50am
From: Charlotte Yaciw
YACIW
Dept: HFD-550 CRP2 N310
Tel No: 301-827-2050 FAX 301-827-2531

Subject: [redacted]oxaprozin

Vickey,

Its no big deal but I think we might mention to Searle that they should correct their stability commitment (document 2117-OXZ-NC-02 dated 12 Sep 1997). The title reads "STABILITY COMMITMENT FOR OXPAROZIN POTASSIUM 600 MG TABLETS". The typo is Searle's, they mispelled the drug name (oops!).

Has John said anything about the trade name issue? Personallv I REALLY dislike the name [redacted], especially for a product with an [redacted]

Charlotte

1 Page(s) Withheld

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__✓__ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

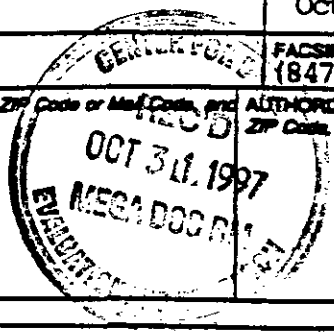
Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
G.D. Searle & Co.	October 30, 1997
TELEPHONE NO. *(Include Area Code)* (847) 982- 8182	FACSIMILE (FAX) Number *(Include Area Code)* (847) 982- 4556
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 4901 Searle Parkway Skokie, Illinois 60077	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, Telephone & FAX number)* IF APPLICABLE



PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-776

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(Trade name)* IF ANY
oxaprozin potassium	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
4,5-Diphenyl-2-oxazolepropanoic acid, potassium salt N-(2-oxo-1,2-diphenylethyl)-succinamic acid, potassium salt

CODE NAME *(If any)* SC-62845

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	600 mg	Oral

(PROPOSED) INDICATION(S) FOR USE
relief of the signs and symptoms of osteoarthritis & rheumatoid arthritis

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

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_____ § 552(b)(5) Draft Labeling

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✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

HFD-550/V Lutwak

Minutes

Type of Meeting: Teleconference
Topic: Teleconference with the sponsor at Division's request
Subject: ———(oxaprozin potassium)– Data Files
NDA: 20-776
Sponsor: Searle
Date: 10-20-97
Attendees:
FDA: R. Stein, V Lutwak

Searle: P East, S Talwalker

Background

Telecon with sponsor at the request of statistician, R. Stein, in response to data file sent on Oct. 7, 1997.

This meeting addressed a two questions:

1. Study 009, 010, and 016-

2. Searle provided two sets of time for 007 study in algorithm and in real time. For the real times which were needed, we were directed to the raw data sets.

Note: There was a satisfactory conclusion. Searle will provide new sets of data within 24-48hours.

cc:
NDA
DivFile
HFD-550 / R Stein/ V Lutwak/ J E Hyde
HFD-550 / SCSO/ C Koerner

Lutwak 550

Minutes

Meeting: Teleconference Meeting for Clarification

NDA: NDA 20-776
~~~~~~~~(oxaprozin potassium)
Sponsor: Searle

Date: October 1,1997

Attendees:
FDA: Dennis Bashaw, Vickey Lutwak
Searle: Peter East, Aziz Karim, Ken Kowowski

Background
Sponsor requested comments from the Division on the PK/PD Protocol submitted September 9, 1997 for pharmacokinetic/pharmacodynamic modeling.

The PK/PD model will look at the alterations in the kinetic profiles in patients experiencing pain. These profiles may change as a result of the number of dental exactions affecting stress and pain levels.

The model will include the following:

- linear mixed effects modeling ccovariants on PD model
- gender
- body weight
- number of teeth extracted- include if a different covariant

Searle will simulate concentration with mathematical modeling using for drug PK and analgesia using Daypro data files (studies) for the PD where the PD data is missing from the Xopane

Windoc/ Draft minutes/nda/971001xo

cc:
NDA
Div Files
HFD-550 /V Lutwak/C Fang CCK 12/15/97
HFD-880/ D Bashaw
~~~~~~~~

HFD-550/V. Lutwak

Minutes

Type of Meeting: Team meeting

Subject: [redacted] (oxaprozin potassium)
Topic: Team meeting for reviewer's comments

NDA: 20-776
Sponsor: Searle

Date: Sept. 4, 1997
Attendees: C Fang, C Yaciw, J E Hyde, V Lutwak

This team meeting is to report on progress and problems related to reviewing NDA 20-776. PDUFA due date May 19,1998.

Chemistry
A list of deficiencies was faxed to Searle on 8/29/97. The most important concern is that a quantitative test for [redacted] is needed to confirm that the [redacted] oxaprozin potassium.

Environmental: [redacted] will qualify for the categorical exclusion, but the sponsor needs to apply for it and at the same time withdraw the original report from submission 001.
Nomenclature: The name went to the labeling and nomenclature committee. It may get turned down because of [redacted]
EER: The site inspection has been scheduled.
Labeling: The label at submission did not follow the [redacted] which was pointed out to the sponsor in August.

Clinical:
The safety information for epidemiological and literature search, including all foreign markets and clinical and noncllinical has not been submitted after repeated reminders to Searle.
PK/PD: Not present but the review is in progress
To Do:
Call Searle with chemist's request.
Look over annual report for Daypro for safety data NDA18-841.

cc:
NDA
DivFile
HFD-550 /C Fang/ C Yaciw/ J E Hyde/ V Lutwak
HFD-550/ SCSO/ C Koerner

3 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Lutwak 550

Minutes

Meeting: Teleconference Meeting for Clarification

NDA: NDA 20-776
———(oxaprozin potassium)
Sponsor: Searle

Date: August 7,1997

Attendees:
FDA: D Bashaw, A Noory, V Lutwak
Searle:
Rich Spivey, Aziz Karim, Ken Kowowski

Overview / Background: ——— is the potassium salt of Daypro, NDA 18-841, which is currently at the end of Phase 4 studies (reviewers: Rudy Widmark and Assoud Noory) which are under clinical and labeling review. The potassium salt was developed for faster absorption compared to the acid form.

Subject
The telecon was requested by the Division to discuss the PK and PD results and analysis of Study N48-96-06-007.

It was brought to the sponsor's attention that the study results for the concentration and effects of oxaprozin potassium were not complete. There was no formal PK and PD evaluation submitted for review to demonstrate concentration and effect of oxaprozin potassium. The sponsor agreed to ammend the supplement to include this data.

The sponsor will send in a brief protocol to the FDA, and the FDA will respond and make comments.

This additional will not hold up the review.

cc:
NDA 20-776
Div File
HFD-550 V Lutwak, L LoBianco 8/29/97
HFD-880 D Bashaw, A Noory
N:\Lutwak\NDA\20776\970807tc

Wade ? # 7/3/97 Weintraub - HFD-105

Christina Fang will call epi & get a name of a Dr. for a consultation from epi on ______

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

RECEIVED JUN 19 1997 By

Date: JUN 18 1997

From: Medical officer, Epidemiology Branch, HFD-733

Through: Director, Division of Pharmacovigilance and Epidemiology, HFD-730 D Graham for RO'Neill 6/18/97

To: Wiley Chambers, M.D., Director, Division of Analgesic, Anti-inflammatory and Dental Drug Products

Subject: Increased Frequency Report of Stevens Johnson Syndrome and Toxic Epidermal Necrolysis for Oxaprazin

This memorandum addresses the Increased Frequency Report received from Searle on May 22, 1997, for Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN) following treatment with Oxaprazin. Seven reports of SJS/TEN in the period 10/29/96 exceeded the rate for the comparison period of 10/29/95 to 10/28/96. Seale states that the firm is consulting with experts and continuing to monitor SJS/TEN reports.

The following table lists by quarter the frequency of reports of SJS/TEN received for oxaprazin and retreived from the SRS:

Year-QTR	Frequency	Year-QTR	Frequency
1992-4	1	1995-1	2
1993-1	0	1995-2	3
1993-2	1	1995-3	1
1993-3	3	1995-4	0
1993-4	5	1996-1	2
1994-1	1	1996-2	1
1994-2	1	1996-3	2
1994-3	0	1996-4	4
1994-4	0	1997-1	1

No obvious trend of increasing reports of SJS/TEN is noted.

The following table lists the proportion of total reports which are SJS/TEN for oxaprazin and 3 other NSAIDs.

Drug	# SJS-TEN	# Total	SJS-TEN/Total
oxaprazin	28	1749	1.6%
nabumetone	22	2615	0.8%
etodolac	15	1653	0.9%
diclofenac	51	4582	1.1%

Finally, review of the 7 cases of SJS/TEN reported for oxaprazin does not reveal obvious risk factors.

In conclusion, no further action is indicated at this time.

Ray Alderfer, M.D., M.P.H.
Medical Officer

cc: HFD-700/O'Neill
HFD-105/Weintraub
HFD-733/Graham,Chron,Dru DG 6/18/97
HFD-550/Widmark

Consult

Minutes

Type of Meeting: Teleconference
Topic: Teleconference with the sponsor to request the Phase 4 post-marketing safety data for Daypro, NDA 18-841.
Subject:———(oxaprozin potassium)
NDA: 20-776
Sponsor: Searle
Date: 07-17-97
Attendees:
FDA: C Fang, V Lutwak
Searle: Winifred Bagley and Medical Officer from Searle

The purpose for this call was to ask the sponsor to submit all the post-marketing safety summary for Daypro. Christina Fang requested from Searle that the data from all the post-marketing studies and annual reports be collected in a summary form for her. In addition, this was to include all references in literature, epidemiology, and foreign sources. Wyeth Ayerst, the manufacture of oxaprozin, will at Searle's request supply the post marketing data from foreign markets since Daypro is marketed only in the US.

Searle agreed to cooperate with this request and will get back to us mid-week with how they propose to present this data for C. Fang's approval.

Addendum

The purpose of the telecon was to ask the sponsor to submit a post-marketing safety summary for Daypro to facilitate the safety review of oxaprozin potassium, based on the agreement of allowing NDA 20776 to cross reference to safety data of Daypro. Safety data from all sources should be included, i.e., post-marketing clinical trials, spontaneous reports, literature reports, epidemiological studies, and foreign post-marketing experiences. Searle questioned about whether the annual reports and the labeling amendments of Daypro would be sufficient. The answer was that the safety information from annual reports should be summarized accordingly. Searle indicated that Searle does not have the foreign marketing rights of oxaprozin, which belong to Wyeth Ayerst. Searle was asked to obtain the foreign safety data as much as possible.

Searle will respond to this request next week and let division know how the sponsor is going to proceed. C. Fang

---

Submitted by Vickey Lutwak
draft vl/July 017,1997

cc:
saved: N:\NDA\20-776\970717tc

The purpose of the telecon was to ask the sponsor to submit a post-marketing safety summary for Daypro to facilitate the safety review of oxaprozin potassium, based on the agreement of allowing NDA 20776 to cross reference to safety data of Daypro. Safety data from all sources should be included, i.e., post-marketing clinical trials, spontaneous reports, literature reports, epidemiological studies, and foreign post-marketing experiences. Searle questioned about whether the annual reports and the labeling amendments of Daypro would be sufficient. The answer was that the safety information from annual reports should be summarized accordingly. Searle indicated that Searle does not have the foreign marketing rights of oxaprozin, which belong to Wyeth Ayerst. Searle was asked to obtain the foreign safety data as much as possible.

Searle will respond to this request next week and let the division know how the sponsor is going to proceed.

Addendum

Minutes

Type of Meeting: Teleconference
Topic: Teleconference with the sponsor to request the Phase 4 post-marketing safety data for Daypro, NDA 18-841.
Subject: [redacted](oxaprozin potassium)
NDA: 20-776
Sponsor: Searle
Date: 07-17-97
Attendees:
FDA: C Fang, V Lutwak
Searle: Winifred Bagley and Medical Officer from Searle

Sent to doc. file 11/21/97

DRAFT

The purpose of the telecon was to ask the sponsor to submit a post-marketing safety summary for Daypro to facilitate the safety review of oxaprozin potassium, based on the agreement of allowing NDA 20776 to cross reference to safety data of Daypro. Safety data from all sources should be included, i.e., post-marketing clinical trials, spontaneous reports, literature reports, epidemiological studies, and foreign post-marketing experiences. Searle questioned about whether the annual reports and the labeling amendments of Daypro would be sufficient. The answer was that the safety information from annual reports should be summarized accordingly. Searle indicated that Searle does not have the foreign marketing rights of oxaprozin, which belong to [redacted]. Searle was asked to obtain the foreign safety data as much as possible.

Searle will respond to this request next week and let division know how the sponsor is going to proceed. C. Fang

Addendum

Talked to Rich Spivey 07/22/98

Once again told Searle the reviewer request (above) and referred to the above memo. In addition, read to him and cited to him the *CFR* Vol. 21, p112 and 113 iv-vi covering the applicant's job to provide the safety information.

Submitted by Vickey Lutwak
draft vl/July 017,1997

cc:
saved: N:\NDA\20-776\970717tc

HFD-

Minutes

Type of Meeting: Teleconference
Topic: Teleconference with the sponsor to discuss some concerns regarding the filing of Xopane after the team on 07-08-97.

Subject: ———(oxaprozin potassium)
NDA: 20-776
Sponsor: Searle

Date: July 11, 1997

Attendees:
FDA: C Fang, MJ Walling, R Stein, J EHyde, C Koerner, V Lutwak
Searle: Richard Spivey and representatives from Searle

Overview/Background: ———is the potassium salt of Daypro, NDA 18-841, which is currently at the end of Phase 4 studies (reviewers: Rudy Widmark and Assoud Noory) under clinical and labeling review. The postassium salt was developed for greater efficacy compared to the acid form.

- The reason for the teleconference was to bring Searle up-to-date on the reviewer's concerns that the data for oxaprozin potassium presented leaves questions unanswered as to the

In Summary

- The sponsor understood the following: the NDA was fileable but that FDA believes there may be a need for extensive changes to the [redacted] labeling.

- The sponsor ended the teleconference with the promise to send: additional information, reanalysis of data, and more studies to demonstrate claims.

Submitted by Vickey Lutwak

cc:
NDA 20-776
Div Files
HFD-550 C Fang, C Yaciw, J E Hyde, C Koerner, V Lutwak
HFD-725 R Stein
HFD-880 D Bashaw
HFD-105 M Weintraub, MJ Walling

saved: N:\NDA\20776\9700708tc

Lutwak
550

Minutes

Type of Meeting: Team meeting

Subject: ———(oxaprozin potassium)
Topic: Team meeting to review and respond data supplies after teleconference on 06-27-97

NDA: 20-776
Sponsor: Searle

Date: 07-08-97
Attendees:

FDA: C Fang, M Weintraub, R Stein, J E Hyde, C Koerner, V Lutwak

---

Overview/Background: ——— is the potassium salt of Daypro (NDA 18-841) currently at the end of Phase 4 studies (reviewers: Rudy Widmark and Assoud Noory) under clinical and labeling review. The potassium salt was developed for — — the acid form.

The meeting today is to establish that Searle has supplied the protocols and the data to support the claim of —

- Conclusion:

  1. ——— is fileable.

  2. With the data presented to date, a ——— label would state at best that it is . For the treatment of the chronic pain of OA and RA, a single dose of 1200mg is recommended per 24 hours

  3. Possible options for Searle: The sponsor can accept this labeling or do more studies to prove the

- Action:

  Set up a teleconference with the sponsor to review the recommendations of the team.

Note: Make 2 copies of minutes in NDA 20-776 Vol. 1.72 for Christina Fang.
M. Weintraub said that the meeting can be held without him if it is difficult to schedule him in. Mary Jane Walling plans to attend.

Submitted by Vickey Lutwak
N:\Lutwak\NDA\20776\9700708

cc:
NDA 20-776
Div Files
HFD-550 C Fang, C Yaciw, J Hyde, W Coulter, C Koerner, V Lutwak
HFD-725 R Stein
HFD-880 D Bashaw
HFD-105 M Weintraub, MJ Walling

Lutwak 550

Minutes

Meeting: Teleconference Meeting for Clarification

Subject: ——— (oxaprozin potassium)

NDA: NDA 20-776

Sponsor: Searle

Date: June 27,1997

Attendees:
FDA: C Fang, W Chambers, R Stein, JE Hyde, C Koerner, V Lutwak
Searle: Winifred Bagley and others representatives

Overview / Background: ——— is the potassium salt of Daypro, NDA 18-841, which is currently at the end of Phase 4 studies (reviewers: Rudy Widmark and Assoud Noory) which are under clinical and labeling review. The potassium salt was developed for faster absorption compared to the acid form.

Clarification Meeting:

This meeting was requested by Christina Fang to clarify with the company some of her concerns over the clinical data submitted for NDA 20-776, ——— oxaprozin potassium), May 19,1997, after a team meeting on 06-23-97 assessing readiness for filing and completeness and/or lack of completeness of the submission for review by the reviewers (N:\Lutwak\NDA\20-776\970623).

- **Action:**

1. Searle proposed to redo and resubmit the necessary data for review.

2. By the end of next week 7/3/97, Searle will send
   - a study listing
   - a summary
   - and clarification of — . as used in the studies.

3. We will be notified by Winifred Bagely before this is submitted.

Submitted by Vickey Lutwak
N:\Lutwak\NDA\20-776\970627

cc:
NDA 20-776
Div Files
HFD-550 C Fang, C Yaciw, W Chambers, JE Hyde, W Coulter, C Koerner, V Lutwak
HFD-725 R Stein
HFD-880 D Bashaw
HFD-105 M Weintraub/ MJ Walling

LK 8/29/97 MW 9/9/97

HFD-550 / V. Lutwak

Meeting

Type or Meeting: Filing Meeting
Subject: [redacted] (oxaprozin potassium)
NDA: NDA 20-776
Sponsor: Searle

Date: June 23,1997
Attendees:
FDA: C Fang, C Yaciw, W Chambers, R Stein, JE Hyde, W Coulter, D Bashaw, C Koerner, V Lutwak

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Overview / Background: [redacted] is the potassium salt of Daypro, NDA 18-841, which is currently approved and has completed all Phase 4 studies (reviewers: Rudy Widmark and Assoud Noory). These studies are presently under clinical and labeling review. The potassium salt was developed for greater faster onset compared to the acid form.

- Pharm: Because [redacted] (oxaprozin potassium) is like Daypro (oxaprozin acid form), the pharmacologist have no issues or questions.

- Chem:

  1. The Sponsor will not be ready until Aug. 15. Inspection will be ordered after filing (7/20/97). Chemistry is ready to request for inspection of the [redacted] and [redacted] plants.

  2. Insufficient stability data to support to support proposed 24 month expiration date.

  3. Inadequate master list of investigational formulations used or all the PK and Clinical studies. Will be requested.

- Biopharm: No issues.

- Clinical: C. Fang expressed some concern.

  1. There appears to be inadequate data to support the proposed [redacted]

Action: It was decide to set up a teleconference with Searle to clarify the clinical issue.

Note: The Phase 4 studies for Daypro are almost ready and the label review (18-841/SLR-012 June 1996) is almost ready. Arrange with the DOC room to have the volumes of NDA 18-841, Daypro, ready for C. Fang to review.

Note: Refer to teleconference N:\Lutwak\NDA\20776\970627

C. Fang needs the post-marketing data from epidemiology surveillance on adverse events for Daypro NDA 18-841.

Review First Draft Due Dates: Christina--Sept. 15, Dick--Sept. 7, Dennis--Oct. 1, 1997.

Received: Yaciw, Coulter, and Stein.

Submitted by Vickey Lutwak
N:\Lutwak\NDA\20776\970623

cc:
NDA 20-776
Div Files
HFD-550 C Fang, C Yaciw, W Chambers, JE Hyde, W Coulter, C Koerner, V Lutwak
HFD-725 R Stein
HFD-880 D Bashaw
HFD-105 M Weintraub/ MJ Walling

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, & OPHTHALMIC DRUG PRODUCTS (HFD-550)

DATE: June 12, 1995 **FIRM:** G.D Searle

REPRESENTATIVES ATTENDING **SUBJECT:** Benilys - Letter Meeg 20/1947

NAME (PRINT)	SIGNATURE	ORGANIZATION	POSITION/OFFICE
Vickey Lutwak	Victoria Lutwak	FDA HFD-550	Project Manager
Christina Fang	C. Fang	FDA HFD-550	Medical
Laura Lu	L Lu	FDA HFD-725	Statistician
Robert DeLap	R DeLap	FDA HFD 105	Deputy Director
M WEINTRAUB	M Weintraub	FDA HFD 101	Dir. ODS
Sheela Talwalker	Stalwalker	G.D. Searle	Assoc. Dir.
Allison Katz	A Katz	G D Searle	marketing
Michael Kuss	M Kuss	G.D. Searle	Clinical Research
Richard Spivey	Richard Spivey	Searle	Reg. Affairs
Tomas Bacanegra	Tomas S Bacanegra	Searle	Clin Research
Daryl DeKarske	D DeKarske	Searle	Reg. Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. *0910-0297*
Expiration Date: *November 30, 1996.*

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Winifred Begley
Director
Regulatory Affairs
G. D. Searle & Co.
Skokie, IL 60077

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Jerome H. Prahl
Associate Director
Regulatory Affairs
G. D. Searle & Co.
Skokie, IL 60077

3. TELEPHONE NUMBER *(Include Area Code)*
(847) 982-8155

4. PRODUCT NAME
— (oxaprozin potassium)

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER
#3252

7. LICENSE NUMBER/NDA NUMBER
N020776

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES ☒ NO *(See reverse if answered YES)*

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse if answered YES)*

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Winifred M. Begley	Director, Regulatory Affairs	May 19, 1997

FORM FDA 3397 (12/93)

Phase II?

Summary

MEETING WITH SEARLE AND THE PILOT DRUG EVALUATION STAFF

DEVELOPMENT PLAN AND MARKETING OBJECTIVES
FOR NEW OXAPROZIN DRUG PRODUCT

December 16, 1994

[2:00 - 3:00 p.m. (E.S.T.), Parklawn Bldg., Conf. Rm. B]

Searle representatives met with the Pilot Drug Evaluation Staff (PDES) on 12/16/94. The purpose was to discuss and confirm PDES' acceptance of Searle's clinical development plan for the K⁺salt of oxaprozin — as a new drug for — indications: — treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

****

PDES meeting attendees:

Linda Katz, M.D., M.P.H.	Medical Officer
Rosemarie Neuner, M.D., MPH.	Medical Officer
Kent Johnson, M.D.	Medical Officer
Charlotte Yashiw	Chemist
Will Coulter, Ph.D.	Pharmacologist
Dennis Bashaw, Pharm. D.	Biopharmaceutist
Harold Blatt, D.D.S.	CSO Project Manager

Searle meeting attendees:

Tomas Bocanegra, M.D.	Senior Director, Clinical Research - Rheumatology and Gastroenterology
Olivia Coughlin	Project Director, Project Management
Subhash Desai, Ph.D.	Director, Product Strategy and Development
Aziz Karim, Ph.D.	Senior Fellow and Senior Director, Clinical Research
Michael E. Kuss	Associate Director, In-Licensed Products
Donald R. Peckels	Associate Director, Regulatory Affairs
Stacy N. Suberg, Ph.D.	Director, U.S. Regulatory Affairs

****

Mr. Peckels presented the agenda (Attachment A). He provided an overview of the meeting's objectives (Attachment B), adding that a review and finalization of conclusions would be done at the end of the meeting.

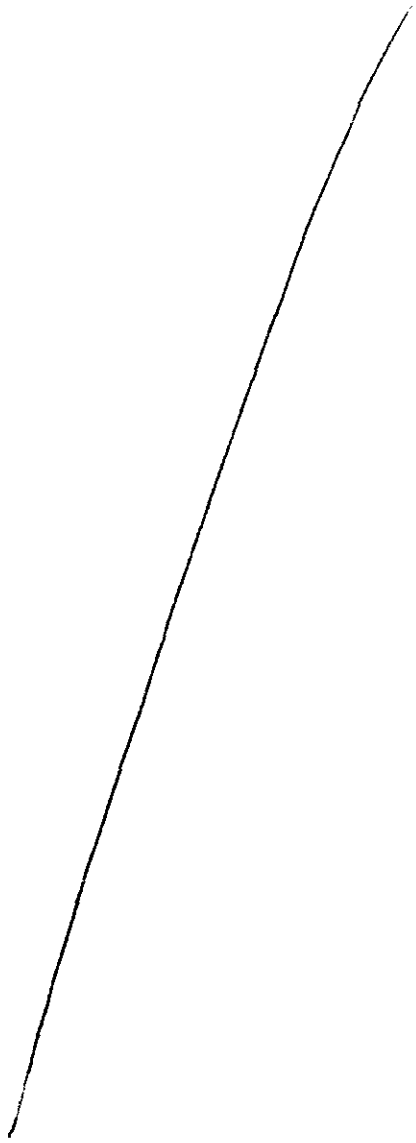
Summary presentations of formulations development, pharmacokinetics, and clinical data from the briefing document were given by Drs. Desai, Karim, and Bocanegra, respectively (Attachments G through I). Highlights were:

1. One formulation will be chosen (the K^+ salt of oxaprozin — — , for clinical development after the pharmacokinetic parameters for both are characterized from the PK study.

2. This PK study may be conducted concurrent with the — —

Mr. Peckels presented a list of six questions sent to Searle from Dr. Neuner on 12/12/94 (Attachment J). These were addressed in addition to others raised to Searle by Dr. Johnson the week of 12/5/94. Highlights were as follows (numbers correspond to those in Attachment J):

1. Searle is seeking the



2. & 3. Searle also seeks approval for OA and RA. Searle explained that clinical safety studies were not necessary because the safety profile of oxaprozin is well characterized and is consistent with that of other propionic acid NSAID products; the small amount of potassium released into the circulation for a single 600 mg dose of the K⁺salt (about 2 mEq) is not expected to present toxicity problems. PDES disagreed. The safety profile of the new formulation (K⁺salt) is not currently known.

Discussions were:

a. Dr. Karim stated Searle was planning to perform a PK/PD dose response study such as PDES requested. Doses would likely include 600 mg QD, 1200 mg QD, and 1800 mg QD.

b. Drs. Neuner and Katz required additional, long-term safety data from a separate study. The efficacy part of the trial should be double-blinded with an open label extension safety part.

Dr. Suberg suggested the data from the efficacy part of the study would be included in the original NDA. The data from the open-label extension portion could be submitted as an NDA amendment. Dr. Katz stated the data cannot be submitted piecemeal because of user fee legislation.

c. Dr. Karim suggested the duration of this study should be determined based upon a review of the safety data generated from the PK and PK/PD studies. This will ensure that a study of adequate duration, to allow long-term use of the drug, is conducted. PDES agreed, adding that PK data alone will only provide safety data for acute administration.

d. Dr. Katz said the worst case scenario would be that the duration of the study would be 12 months. It may be possible to shorten this. She added that the data derived from the PK study may not be sufficient to show long-term safety. She agreed to review the initial PK and PK/PD safety data before the duration of the safety study is determined.

e. Dr. Bashaw recommended Searle perform the PK/PD study to steady state to allow for the extrapolation to long-term safety. He also recommended that the number of samples taken immediately post-dose be increased to ensure adequate characterization of the time/concentration profile.

4. An animal toxicity study will not be needed because Searle will perform a clinical safety study. Mr. Peckels pointed out that the animal toxicity study was originally proposed to confirm that the GI irritation of oxaprozin, whether administered as oxaprozin acid or the potassium salt, is essentially the same.

5. Searle was planning to submit the protocols to PDES for comment prior to initiating the studies.

Mr. Peckels stated that the meeting's objectives need to be readdressed with our conclusions; he presented an earlier overhead (Attachment B). Dr. Suberg concluded by stating:

1. Searle will conduct the following clinical studies:

   a. PK single-dose study: to help in choosing the formulation with which to proceed.

   b. PK/PD dose-ranging study (performed to steady-state): to obtain optimal dosage information and provide short-term safety data.

   c. [redacted]

   d. One safety/efficacy study in patients with OA: to assess the long-term safety of the new drug. The study will be double-blinded, followed by an open label extension. The duration of the open label portion will be negotiated with the FDA after data from the PK and PK/PD studies are reviewed and submitted to PDES.

2. Market exclusivity will be granted based upon performance of the required clinical studies.

   [Although it was not specifically stated, market exclusivity for OA and RA will be granted based on the need to assess the clinical safety and efficacy of the new drug.]

No further discussions ensued, and the meeting adjourned.

/S/
Donald R. Peckels

Meeting Report Addendum

Members of the Pilot Drug Evaluation Staff reviewed the draft meeting report prepared by Searle and provided comments to Searle on January 30, 1995. With the following two exceptions, Searle incorporated PDES' comments into the final meeting report (12/16/94). These exceptions were:

Clarification of these issues and other clinical study information relevant to this IND was discussed and agreed upon at a teleconference meeting on February 1, 1995 between members of PDES and Searle. Meeting participants were:

SEARLE	PDES
Dr. Tomas Bocanegra	Dr. Dennis Bashaw
Dr. Subhash Desai	Dr. Harold Blatt
Ms. Olivia Coughlin	Dr. Linda Katz
Mr. Donald Peckels	Dr. Rosemarie Neuner

The issues discussed and conclusions reached are summarized below:

3. Arthritic Studies/Market Exclusivity

Dr. Neuner stated that at the December 16, 1994 meeting, PDES did not realize that Searle was pursuing indications for OA and RA for oxaprozin potassium PDES now made it clear that in order to obtain indications for OA and RA, a 6-month (minimum) safety study is required for each indication. A safety study in each indication was requested because of the difference in etiology between OA and RA patients.

To obtain the required safety information and approval of the indications, Dr. Katz informed us that Searle would need to conduct a safety study of a minimum 6 months' duration in OA patients and a safety study of a minimum 6 months' duration in RA patients. Both studies should include Daypro as an arm. The patient number criteria in each arm for these safety studies are:

OA: 300 patients

RA: 90 patients

A separate discussion ensued regarding market exclusivity. PDES indicated that OA and RA efficacy trials are not required unless Searle wanted exclusivity for these indications. In that case, adequate, well-controlled, double-blind efficacy studies are required.

Searle will submit protocols of the proposed OA and RA studies to PDES for review and comment prior to study initiation.

/S/
Donald R. Peckels

MEETING MINUTES

NDA 18-841 12-16-94 3rd Floor, Conf. Rm."B" Parklawn Bldg.

Oxaprozin

BETWEEN: FDA; HFD-007 STAFF

Linda Katz, M.D., M.P.H., Medical Officer
Rosemarie Neuner, M.D., M.P.H., Medical Officer
Kent Johnson, M.D., Medical Officer
Charlotte Yaciw, Chemist
Dennis Bashaw, Ph.D., Phamacokineticist
Will Coulter, Ph.D., Pharmacologist
Harold Blatt, D.D.S., CSO

AND

G.D. Searle and Co.

Tomas Bocanegra, M.D., Sr. Director, Clin. Research
Olivia Coughlin, Project Mgr.
Subash Desai, Ph.D., Dir., Product Strategy and Devel.
Aziz Karim, Ph. D., Clin. Research
Michael Kuss, Clin. Research
Stacy Suberg, Ph.D., Dir. Reg. Affairs
Don Peckels, Reg. Affairs

First a brief overview was presented by Searle.

There were two major objectives in development.

1. to increase the onset of action and for this pupose they chose a Potassium salt.
2. formulation development.
   A. oxaprozin as a potassium salt.
   B.

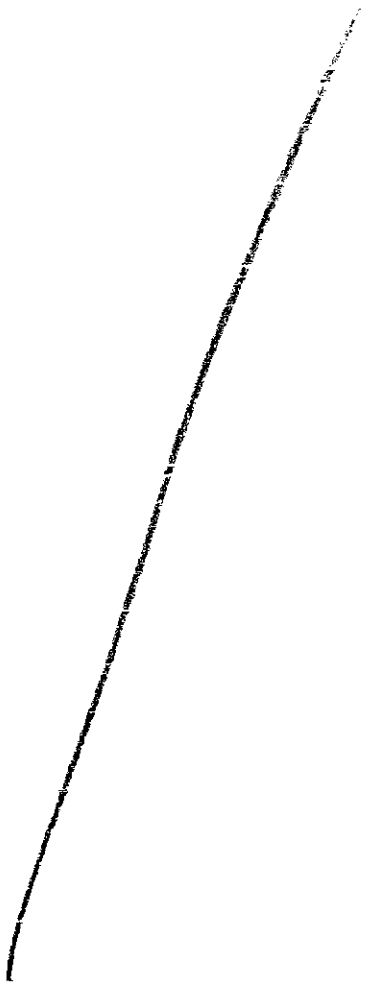
The rationale for the potassium salt was to increase both the rate of absorption and the onset of action while the total exposure remains the same. They expect the safety to be the same for the salt as for the acid.

Dr. Katz was concerned that the safety profile is the same. When you change formulation you are not sure about the safety profile. As a combination you are not just adding potassium. We will need safety information especially in product thast will be used in RA and OA for long term use. But we will need to see long term safety studies if you are going for RA and OA indications. Such a safety study will be determined by PK/PD studies. Such a safety study would last 6 mos to 1 year. Also we

want everything (all studies including the long term safety study) finished when the NDA is submitted because we only have 12 mos to complete our review. We can get back together after the dose response trial and the PK/PD data is done.

Dr. Bashaw noted that as part of the presentation they gave a single dose PK trial. Can this be converted to steady state? Dr. Karimi said that steady state C bar value should be the same. He also stated that the dose-response trial in healthy volunteers was a good idea. They already have a large amount of steady statte data on oxaprozin acid.

Mr. Peckels stated they would submit the PK studies and evaluate at that time. He also stated that an animal study may not be needed and they are not planning an endoscopy study. Dr. Bashaw stated that they have to understand the kinetic dynamics of the old oxaprozin product.



Dr. Bashaw wanted the sponsor to front load in PK studies with more samples.

Mr. Peckels recapped.

s. Request to wait after PK/PD trial to determine length of safety trial for OA and RA.

Dr. Johnson again asked if there was any rationale for using dogs. Dr. Coulter replied that dog toxicity studies don't correlate well with humans but a comparison of potassium salt to free acid in dogs will show you which form is more toxic.

Meeting was closed by Mr. Peckels.

41 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

000-00002

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached list of investigators	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Daryl DeKarske	Sr. Associate, Worldwide Regulatory Affairs
FIRM/ORGANIZATION: G.D. Searle & Co.	
SIGNATURE	DATE: 3/10/00

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

000-00004

Investigator Financial Disclosure - Form FDA 3454
Study N48-98-02-022

Principal Investigator: Alan J. Kivitz, MD
Subinvestigator(s):

/

Principal Investigator: William S. Makarowski, MD
Subinvestigator(s):

—

Principal Investigator: F. Gilbert McMahon, MD
Subinvestigator(s):

/

Principal Investigator: Naomi De Sola Pool, MD
Subinvestigator(s):

/

Principal Investigator: Maurice Archuleta, MD
Subinvestigator(s):

—

Principal Investigator: Marshall R. Sack, MD
Subinvestigator(s):

/

Principal Investigator: Joy Schechtman, DO
Subinvestigator(s):

—

Principal Investigator: Mark E. Kutner, MD
Subinvestigator(s):

/

Investigator Financial Disclosure - Form FDA 3454
Study N48-98-02-022

Principal Investigator: David H. Sikes, MD
Subinvestigator(s):

/

Principal Investigator: Kevin L. Tack, MD
Subinvestigator(s):

/

Principal Investigator: Robert G. Trapp, MD
Subinvestigator(s):

Principal Investigator: Edward Portnoy, MD
Subinvestigator(s):

/

Principal Investigator: Nathan Wei, MD
Subinvestigator(s):

Principal Investigator: Stuart S. Kassan, MD
Subinvestigator(s):

/

Principal Investigator: Howard L. Offenberg, MD
Subinvestigator(s):

/

Principal Investigator: Patrick H. Peters, Jr., MD
Subinvestigator(s):

/

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Dr. E. Robert Harris (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study N48-98-02-022 (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Daryl DeKarske	Sr. Associate, Worldwide Regulatory Affairs
FIRM/ORGANIZATION: G.D. Searle & Co.	
SIGNATURE	DATE: 3/10/00

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

SEARLE

CERTIFICATION/FINANCIAL DISCLOSURE FORM

Financial Disclosure by Clinical Investigators

Please complete all of the information below and retain a copy of this form for your records.

1. Study Name: Oxaprozin Potassium 1200-1800 mg QD Analgesic Duration and Safety in Osteoarthritis of the Knee
2. Protocol number: N48-98-02-022
3. Investigator ☑ Subinvestigator ☐
4. Investigator/Subinvestigator Name:

   Institution Name (if applicable):
5. Address:
6. Telephone:
8. Indicate by marking YES or NO if any of the financial interests or arrangements of concern to FDA (and described below) apply to you, your spouse, or dependent children:

YES	NO	
☐	☑	Financial arrangements whereby the value of the compensation could be influenced by the outcome of the study. This should include, for example, compensation that is explicitly greater for a favorable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product, such as a royalty interest. If yes, please describe:
☐	☑	Significant payments of other sorts, excluding the costs of conducting the study or other clinical studies. This could include, for example, payments made to the investigator or the institution to support activities that have a monetary value great than $25,000 (i.e., a grant to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria). If yes, please describe:
☐	☑	A proprietary or financial interest in the test product such as a patent, trademark, copyright, or licensing agreement. If yes, please describe:
☑	☐	A significant equity interest in the sponsor of the study. This would include, for example, any ownership interest, stock options, or other financial interest whose value cannot be easily determined through reference to public prices, or an equity interest in a publicly traded company exceeding $50,000. If yes, please describe: Common stock

OR

☐ I hereby certify that none of the financial interest or arrangements listed above exist for myself, my spouse, or my dependent children.

In accordance with 21 CFR Parts 54.1 to 54.6, I declare that the information provided on this form is, to the best of my knowledge and belief, true, correct, and complete. Furthermore, if my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of the study or within one year after the last patient has completed the studies specified in the protocol, I will notify Searle promptly.

Signature: _____ 10. Date: 2-25-99

1/8/99

000-00008

Steps Taken to Minimize the Potential for Bias

Protocol # N48-98-02-022

Study Title A Multicenter, Double-Blind, Placebo Controlled, Randomized Parallel Group Study of the Analgesic Duration and Safety of Oxaprozin Potassium 1200-1800 mg Daily in Patients with Osteoarthritis of the Knee

Our standard operating procedure is to follow the current FDA Good Clinical Practices. Monitors frequently visit individual study sites, and individual site audits are conducted. This randomized, double-blind study was conducted under strict scientific principles, and was conducted at multiple sites with multiple investigators, most of whom had no disclosable financial interest.

We also monitor the current FDA listing: "Disqualified/Restricted/Assurances List For Clinical Investigators".