CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-776

MEDICAL REVIEW

MEDICAL OFFICER'S REVIEW

NDA Number:	20-776
Date submitted	April 19, June 14, October 1, and October 11, 2002
Drug Name:	Oxaprozin potassium 600mg tablet
Trade Name:	Daypro ALTA™
Sponsor:	G.D. Searle LLC 4901 Searle Parkway Skokie, IL 60077 Susan Tegtmeyer (Manager, Global Regulatory Affairs) Tel: 847-982-8811 Fax: 847-982-8090
Drug Category:	Anti-inflammatory
Indication:	Rheumatoid arthritis and osteoarthritis
Drug Class:	NSAID
Medical Reviewer:	Christina Fang, M.D.
Secondary Reviewer:	James Witter, M.D., Ph.D.
Final Review Date:	October 15, 2002
Related Reviews:	Chemistry, DDMAC, and OPDRA
CSO Contact:	Nancy Halonen

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1. Background information

This is the fourth major submission to the original NDA 20-776 for oxaprozin potassium. The key information about the first three submissions was summarized in the medical review dated June 11, 2001 and will not be repeated here. The purpose of the submission on April 19 was to finalize the labeling as a response to the Division's recommendations stated in the action letter dated December 21, 2001. The submission on June 14 included a proposal of the new brand name Daypro ALTA.

2. Review of the labeling

The Sponsor has made several changes to the labeling in accordance with the Division's recommendations. However, some labeling statements in the Clinical Studies section and Adverse Events section are not considered acceptable and are outlined below:

2.1. The statement in reference to — , in the Clinical Studies section is not considered appropriate and should be revised as the following: "With respect to GI events, Daypro ALTA appeared to be less well tolerated than oxaprozin acid in this study. The rates for symptomatic ulcers (2.2%) and nausea (13%) for Daypro ALTA treated patients —
— were higher than the rates observed with oxaprozin acid (0% and 6%, respectively)."

The findings reported in the Clinical Studies section are based on the data analysis of a controlled trial, in which oxaprozin and oxaprozin potassium were the only 2 arms of active treatments with no other NSAID drugs included. The statement about —
is neither valid nor relevant here.

2.2. The —
—
— , is not considered acceptable. One of the major reasons for using the NSAID template is the observed similarity between the drugs in the class in terms of their pharmacological activities. The safety database on oxaprozin potassium is very limited. The maximum exposures included a 24-week exposure to 1200mg in about 300 subjects (in the two 24-week OA trials, one with and one without controls); a 2-week exposure to 1800mg in 60 subjects; any exposure to the drug in less than 1800 subjects. When the specific events listed in

the NSAID's class labeling were less frequently or not reported in the studies of oxaprozin/oxaprozin potassium, it does not mean that the potential risks for patients taking oxaprozin products to have similar events are much smaller. Using GI ulcer as an example, symptomatic/bleeding ulcer were reported in 0.8 to 2.2% of patients receiving oxaprozin potassium versus zero percent in the active control arms in the 4 controlled OA studies. The rate of asymptomatic ulcer could not be determined because patients were not followed by endoscopic evaluations in these studies. Another example is melena ( ). Melena was reported in 1% of about 300 patients on oxaprozin potassium in the 24-week controlled OA trial and in 2% of about 400 patients who were treated with oxaprozin for 4 to 8 weeks in 5 post-marketing clinical trials. Therefore, should be removed from the adverse event section.

3. Addendum

The reviewer's comments were discussed and accepted by the Sponsor at a teleconference on September 23, 2002. The corresponding labeling changes were reflected in the submission dated October 1, 2002. In addition, the comments provided by the Division of Medication Errors and Technical Support of the Office of Drug Safety were forwarded to the sponsor (refer to the review by Hye-Joo Kim dated August 14, 2002). The precaution about not to use Daypro ALTA concomitantly with other oxaprozin-containing products was added to the labeling in the latest submission dated October 11, 2002.

4. Conclusion and recommendations

The latest version of the revised labeling submitted on October 11, 2002 is considered acceptable and is recommended for approval.

Christina Fang, M.D. Date

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HFD-550/C. Fang/R. Puttagunta/N. Halonen
HFD-340

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

MEDICAL OFFICER'S REVIEW

NDA Number:	20-776
Date submitted	June 11, 2001
Drug Name:	Oxaprozin potassium 600mg tablet
Trade Name:	Daypro
Sponsor:	G.D. Searle & Co. 4901 Searle Parkway Skokie, IL 60077 Susan Tegtmeyer (Associate, Regulatory Affairs) Tel: 847-982-8811 Fax: 847-982-8090
Drug Category:	Anti-inflammatory
Indication:	Rheumatoid arthritis and osteoarthritis
Drug Class:	NSAID
Medical Reviewer:	Christina Fang, M.D.
Secondary Reviewer:	Larry Goldkind, M.D.
Review Date:	December 9, 2001
Related Reviews:	Chemistry, DDMAC, and OPDRA
CSO Contact:	Carmen Debellas

Christina Fang, M.D. Date

Deputy Director Date

CC: Original NDA 20-776
HFD-550/Division File
HFD-550/C. Fang/R. Puttagunta/C. Debellas
HFD-340

Background information

The original NDA 20-776 for oxaprozin potassium was submitted on May 19, 1997 for the indications of [redacted] of signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA). It was deemed approvable for OA and RA indications at a dosing regimen of 1200mg daily. The recommendation was based on the demonstration of steady state bioequivalence between the acid (Daypro®) and the salt formulations and the efficacy results of the 24-week, placebo-controlled OA study, in which the 2 formulations were compared (refer to the medical review dated May 20, 1998 for detail). [redacted] indication was not approved because [redacted]

The major amendment to the original NDA submitted on January 21, 2000 was again deemed approvable for the OA and RA indications but not [redacted] indication.

Drug exposure to oxaprozin potassium ranged from any exposure in 1761 subjects to a 24-week exposure in 306 subjects. Exposure to oxaprozin potassium 1800mg given as a single dose or as a split dose (1200mg followed by 600mg) ranged from any exposure in 288 subjects (in four studies) to a two-week exposure in 60

subjects. Remarkable cases of symptomatic ulcer and gastrointestinal (GI) bleed were summarized in the table below:

Multiple-dose studies (≥2 wks)	*Cases (#subjects exposed to oxaprozin potassium, rate of event)*	*Cases (control group, #subjects)*
Oxaprozin potassium at 1200mg a day		
24-week OA (#006)	6 cases of symptomatic ulcer and 1 case of ulcer with slight bleeding (322 subjects, 2.2%)	None (oxaprozin acid 1200mg/d, 320 subjects)
6-week OA (#014)	1 case of hemorrhagic and symptomatic ulcer with melena (124 subjects, 0.8%)	None (etodolac 400mg bid, 127 subjects)
6-week OA (#015)	1 case of melena (126 subjects, 0.8%)	None (etodolac 400mg bid, 126 subjects)
24-week OA (#017)	None (189 subjects; 123 completed 24 weeks)	No control group
Oxaprozin potassium at 1200-1800mg a day		
2-week OA (#022)	1 case of symptomatic ulcer and gastritis on 1800mg taken as a single dose (79 subjects, 1.4%); 1 case of melena on 1200mg followed by 600 flexible dosing (167 subjects, 0.6%); Total rate: 0.8% (2/246)	None (ibuprofen 400mg/d, 82 subjects)

In the 24-week OA study symptomatic ulcer cases were reported in 2.2% of the subjects on oxaprozin potassium, but none of the subjects on oxaprozin. Also, the oxaprozin potassium group had statistically significantly more reports of nausea (13% versus 6%) than the oxaprozin group. In general, the salt formulation of oxaprozin appeared to be less well tolerated than the acid formulation as reflected in the overall GI adverse events, specific upper GI events, and early terminations from the study due to GI events.

Because of the limited exposure to oxaprozin potassium 1800mg per day and anticipated dose-related GI toxicity (as suggested by safety data from the studies of Daypro 1800mg) the maximum daily dose of oxaprozin potassium is recommended not to exceed 1200mg as compared to the 1800mg maximum daily dose of oxaprozin.

In the current amendment to the NDA the sponsor submits a revised draft labeling for OA and RA indications.

Labeling modifications proposed by the sponsor

The brand name of the product is changed from Benilas to Daypro — or Daypro

The statements in the clinical study section under osteoarthritis are reworded to: "Daypro — 1200 mg once daily was evaluated for the relief of the signs and symptoms of osteoarthritis in a 6-month placebo-controlled study versus oxaprozin acid in over 300 patients. In this trial, treatment with Daypro — resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. Daypro — demonstrated significant reduction in joint pain compared to placebo and was found to be comparable to 1200 mg once daily of oxaprozin acid."

The statement: "— — under the section of drug interaction with methotrexate is deleted.

Other changes of the labeling statements are minor and are basically for the purpose of clarification; e.g., alopecia — from the rare adverse event (AE) section —

Discussion

Based on the safety data on oxaprozin potassium (9 cases of symptomatic ulcer and 2 cases of melena versus none in the control groups), especially the findings from the 24-week OA study (7 cases of symptomatic ulcer versus none in the oxaprozin group), the apparent difference in GI tolerance between the salt and acid formulations is considered valuable information to be included in the labeling.

The modifier — in the brand name Daypro — is considered misleading because it could be potential misinterpreted as " — ". Daypro K 600mg could be easily confused with — 600mg because they sound alike, especially when the drug is prescribed over the phone.

The proposed labeling statements in the section of clinical study of osteoarthritis are considered acceptable because oxaprozin potassium was shown to perform statistically better than placebo in terms of knee pain and WOMAC (pain, stiffness, and physical function) and was comparable to oxaprozin acid based on the analysis using Q-statistics in the 24-week OA study.

The deletion of the statement about the — — is considered acceptable because human data on

the drug interaction between oxaprozin and methotrexate were already included in the labeling and are considered more appropriate for the section.

The [redacted] is omitted in comparison with Daypro labeling.

In addition, there are a number of comments from the Office of Post-Marketing Drug Risk Assessment (OPDRA), basically for minimizing potential confusion between the two formulations of oxaprozin and for clarification and better format of the unit-dose, container, and carton labels.

Conclusion and recommendations

The proposed brand names Daypro [redacted] and Daypro [redacted] are not considered acceptable. At this time the application is approvable as the established name, oxaprozin potassium 600mg tablet, with the labeling submitted by the sponsor (see attachment), provided that the following revisions should be made to the labeling:

1. The sponsor is advised to submit new brand names for review.

2. The following statements should be added to the end of the paragraph in the clinical study section under OA: [redacted]

3. The precaution statements for photosensitivity should be reinserted.

4. Under the section of description it should be "structural formula" instead of "structured formula".

5. The dosage form "tablets" (which is missing from the established name in the proposed labeling) should be included as part of the established name (where [redacted] is not an official dosage form).

7. For the unit-dose label the prominence of the established name should be increased [21 CFR 201.10 (g)(1) and (2)] and the dosage form (tablet) should be included.

8. For the container label and carton label the recommendations are

MEDICAL OFFICER'S REVIEW

NDA Number:	20-776
Date submitted	January 21, 2000
Drug Name:	Oxaprozin potassium 600mg tablet
Trade Name:	Benilas™
Sponsor:	G.D. Searle & Co. 4901 Searle Parkway Skokie, IL 60077 Winifred Begley (Director, Regulatory Affairs) Tel: 847-982-8155 Fax: 847-982-8090
Drug Category:	— anti-inflammatory
Indication:	—
Drug Class:	NSAID
Medical Reviewer:	Christina Fang, M.D.
Secondary Reviewer:	Karen Midthun, M.D.
Review Date:	July 19, 2000
Related Reviews:	Statistics
CSO Contact:	Sharon Schmidt

Christina Fang 7/24/00 — Christina Fang, M.D. Date

Division Director Date

CC: Original NDA 20-776
HFD-550/Division File
HFD-550/C. Fang/S. Schmidt/L. Lu
HFD-340
R/D Init. by:
F/T by:

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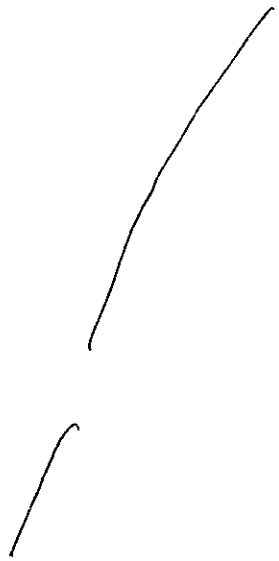
I. OVERALL SUMMARY

1. Background information

The original NDA 20-776 for oxaprozin potassium, or Benilas™ was submitted in May 1997 for the indications of — of signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA). It was deemed approvable for OA and RA indications at a dosing regimen of 1200mg daily based on the steady state bioequivalence between the acid (Daypro®) and the salt formulations and the results of the 24-week, placebo-controlled OA study, in which the 2 formulations were compared (refer to medical review dated May 20, 1998 for details). — indication was not approved because —



3. Safety

Total exposure: A total of 1761 subjects were exposed to at least a single dose of oxaprozin potassium at 1200mg or 1800mg level, including 626 in 12 single-dose studies, 128 in 1-week PK and low back pain studies, 246 in 2-week OA studies, 250 in 6-week OA studies, and 511 in 24-week OA studies.

Exposure to 1800mg: Drug exposure to 1800mg oxaprozin potassium given as a single dose or as a split dose (1200mg followed by 600mg) is summarized in the table: 288 subjects had a single day exposure; 60 had daily exposure for 2 weeks.

Cumulative exposure to 1800mg (days)	***1800mg single dose***		***1200mg + 600mg***			***Total***
	Single-dose PK study 008	***2-wk OA study 022***		***1-week LBP study 019***	***Single-dose dental study 007***	
≥1	36	79	79	74	20	288
≥2		73	53*	42*		168
≥3		71	44*	21		136
≥4		70	35*			105
≥7		65	18*			83
14		55	5			60

*Note: the exposure to 1800mg in the flexible dosing group was not counted over consecutive days, but the total number of days exposed.

Exposure to 1200mg: Longer-term exposure to 1200mg oxaprozin potassium is summarized in the table: about 300 subjects were exposed for 24 weeks.

Cumulative exposure to 1200mg (weeks)	*Multiple-dose OA trials*				
	24 weeks study 006	*6 weeks study 014*	*6 weeks study 015*	*24 weeks* study 017*	*Total*
<2	322	124	126	189	761
≥2	280	119	124	185	708
≥6	232	92	103	175	602
≥12	212			161	373
≥18	193			136	329
24	183			123	306

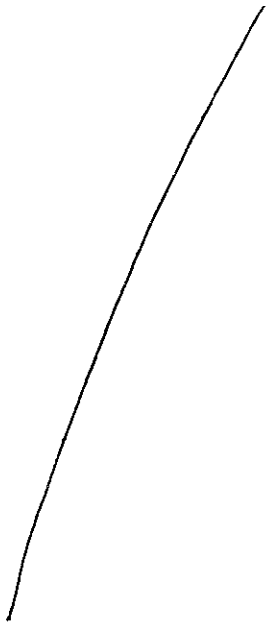
*Note: Studies 006, 014, and 015 were placebo- and active-controlled studies and study 017 had no control groups.

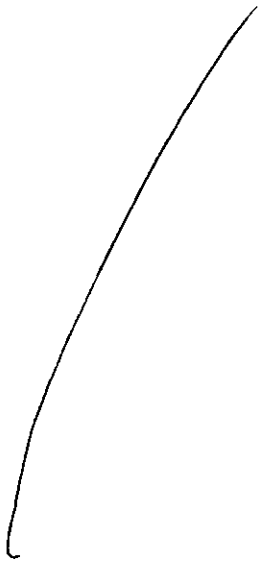
Upper GI distress symptoms: Subjects in the oxaprozin potassium treatment groups, in the short-term multiple-dose studies at 1200 to 1800mg as well as the longer-term multiple-dose studies at 1200mg, had significantly more reports of GI symptoms, especially upper GI distress symptoms than placebo or active controls (ibuprofen, etodolac) and remarkably more early terminations from the study due to the specific upper GI distress symptoms than the control groups.

GI ulcer and bleeds at 1200mg: In the 24-week controlled OA study there were 7 ulcer cases: 6 were symptomatic and one of the six had slight bleeding, all reported in the oxaprozin potassium group versus none in the oxaprozin acid group. In one of the two 6-week controlled OA studies there was a case of hemorrhagic gastric ulcer and gastritis accompanied by GI distress symptoms and melena in a patient after 9 days of oxaprozin potassium treatment. In the second 6-week OA study there was also a case of melena. There were no cases of gross GI bleeds reported in 24-week, open-label study. The explanation provided by the sponsor is the mandatory requirement of taking the medication with the evening meal in the open-label study.

GI ulcer and bleeds at 1800mg: In the 2-week study of oxaprozin potassium at 1200 to 1800mg levels there was 1 case of symptomatic duodenal ulcer and gastritis in the 1800mg group and 1 case of melena in the 1200 to 1800mg group.

In general, the salt formulation of oxaprozin was shown to cause higher rates of GI ulcers and ulcer complications than the acid formulation and the GI toxicities associated with the use of oxaprozin potassium appeared to be dose-related.





5. Recommendations

This application is not recommended to be approvable for

II. TWO-WEEK OA STUDY OF 1800MG OXAPROZIN POTASSIUM
(NDA volumes 4-8)

1. Protocol (study 022)

The key features of the protocol are presented in the table below:

Study objective	Analgesic duration of oxaprozin potassium 1200mg to 1800mg dosing; Safety of oxaprozin potassium 1800mg daily dose for 14 days
Study design	Multiple-dose, randomized, double-blind, placebo- and active treatment-controlled, parallel, 24-center
Study population	Male and female adult subjects with a minimum of 6-month history of osteoarthritis of the knee (by ACR criteria and confirmed by a weight-bearing x-ray) and with at least moderate baseline OA symptoms, a Functional Capacity Classification of I-III, who underwent a washout of all NSAIDs and other analgesics and had no other joint conditions or concurrent medication that could potentially interfere with the efficacy evaluation of the test drug
Treatment and dosing	Oxaprozin potassium 1800mg, oxaprozin potassium 1200mg to 1800mg (an optional dose of 600mg to be taken as needed at least 2 hours after 1200mg dose), ibuprofen 400mg, or placebo daily for 14 days.
Baseline condition	Pain intensity (PI) ≥5 on a 10-point scale and increased by at least 2 points from screening, knee pain on weight-bearing ≥3 on a 5-point scale and increased by at least 1 point from screening, WOMAC pain index ≥9 on a 20-point scale, and patients' global ≥3 on a 5-point scale
Efficacy assessment	Primary: PI score on a 10-point scale at 24 hours, proportion returning to baseline PI at 24 hours, time to remedication and proportion taking remedication; Secondary: PI on days 2, 3, 7, and 14, pain relief (PR) at 24 hours, patients' global; Exploratory: knee pain on weight-bearing, WOMAC (pain section only), PI and PR at 1.5, 15, 18, and 21 hours after the initial dose
Safety assessment	Report of treatment-emergent adverse events (AE); Routine laboratory tests (biochemistry and hematology), vital signs, and physical examinations at baseline and day 14 (or the time of early termination)

Note: ACR stands for American College of Rheumatology; WOMAC for the Western Ontario McMaster Arthritis Center.

2. Demographic and other baseline characteristics

The study population consisted of 491 subjects who received the treatments, with an age range of 28 to 91 years and a mean around 60 years, 78% Caucasian, 11% African American, 9% Hispanic, and 70% females. There were no statistically significant differences between the four treatment groups with regard to demographic characteristics such as age, gender, race, height, and weight, with regard to baseline vital signs (except that subjects in the oxaprozin potassium 1200mg to 1800mg group had significantly lower pulse, 71 versus 74 per minute, than the other groups), and with regard to the other baseline status such as PI, knee pain on weight-bearing, WOMAC pain index, patients' global, OA functional class, and index joint, except that subjects in the oxaprozin potassium 1200mg to 1800mg group had significantly longer disease duration (10 versus 8 years) than the other groups.

3. Study execution and drug exposure

The intent to treat population consisted of 81 subjects in the oxaprozin potassium 1800mg group, 168 subjects in the oxaprozin potassium 1200mg to 1800mg group, 82 subjects in the ibuprofen 400mg group, and 160 subjects in the placebo group. There were 28 cases of violation of the protocol defined eligibility criteria as shown in the table below:

Eligibility violations	***Oxaprozin K^+ 1800mg n=81***	***Oxaprozin K^+ 1200-1800mg n=168***	***Ibuprofen 400mg n=82***	***Placebo n=160***
Shorter duration of OA	0	2	0	0
Lower baseline symptom severity	4	5	2	4
Medical conditions not allowed	1	0	0	1
Deviation of laboratory values	1	3	1	1
Took analgesics not allowed in specified time windows	0	0	1	2
Total	6 (7%)	10 (6%)	4 (5%)	8 (5%)

Other protocol violations included deviations from the protocol defined statistical analysis and inadequate data collection and analysis with regard to certain lab tests such as alkaline phosphatase, bilirubin, and BUN.

The cases of early termination are summarized in terms of the treatment groups and the reasons for early termination as shown in the table below.

Reasons for the early termination from the study	***Oxaprozin K⁺ 1800mg n=81***	***Oxaprozin K⁺ 1200-1800mg n=168***	***Ibuprofen 400mg n=82***	***Placebo n=160***
Lack of efficacy	8 (10%)	17 (10%)	12 (15%)	32 (20%)
Lost to follow up	1 (1%)	0	0	1 (<1%)
Non-compliance	8 (10%)	4 (2%)	2 (2%)	4 (3%)
Adverse events	11 (14%)	16 (10%)	3 (4%)	12 (8%)
Total	28 (35%)	37 (22%)	17 (21%)	49 (31%)

There was a total of 360 subjects (73%) who completed the study: 65% in the oxaprozin potassium 1800mg group, 78% in the oxaprozin potassium 1200mg to 1800mg group, 79% in the ibuprofen 400mg group, and 69% in the placebo group.

The extent of cumulative drug exposure per treatment group is summarized in the table below.

Cumulative exposure (days)	***Oxaprozin K⁺ 1800mg n=81***	***Oxaprozin K⁺ 1200-1800mg n=168***	***Ibuprofen 400mg n=82***	***Placebo n=160***
≥1	79 (98%)	167 (99%)	82 (100%)	159 (99%)
≥2	73 (90%)	164 (98%)	77 (94%)	155 (97%)
≥3	71 (88%)	160 (95%)	75 (91%)	153 (96%)
≥4	70 (86%)	156 (93%)	74 (90%)	144 (90%)
≥7	65 (80%)	146 (87%)	70 (85%)	124 (78%)
14	55 (68%)	132 (79%)	66 (80%)	114 (71%)

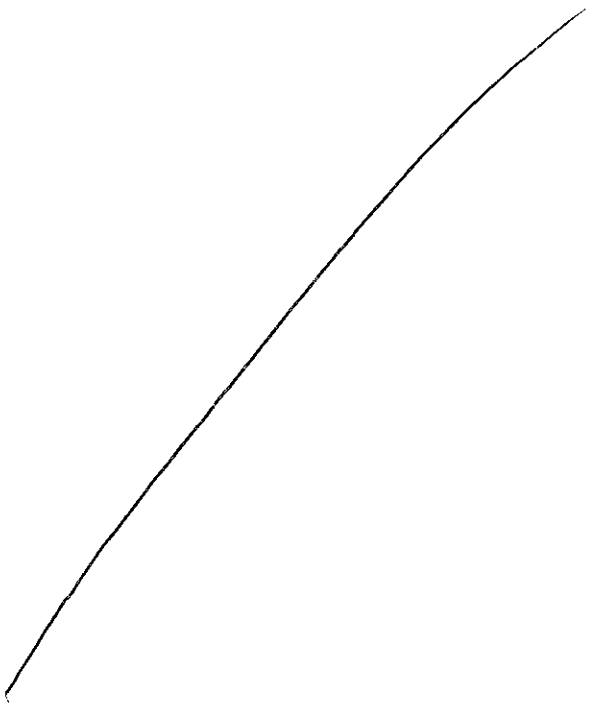
The extent of drug exposure to 1800mg oxaprozin potassium is summarized in the table by placing the subgroup that actually had the additional 600mg dose in the flexible dosing group and the 1800mg fixed dosing group together. In the flexible dosing group ten subjects had two 600mg doses taken on the same calender day as the 1200mg daily dose, translating to a total of 2400mg within a 24-hour period.

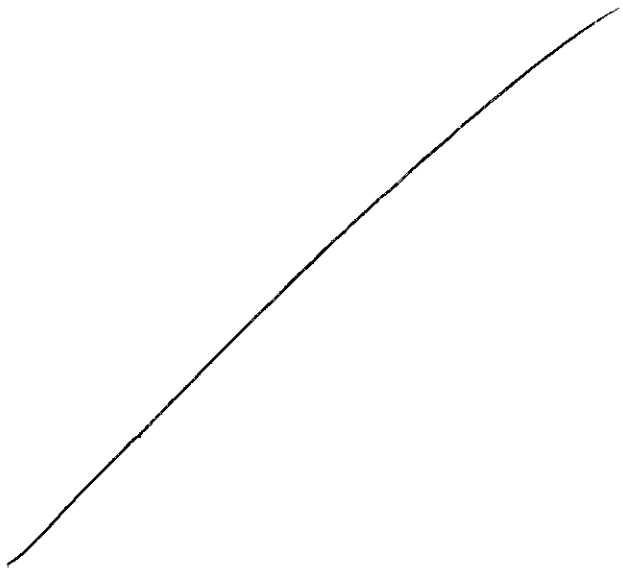
Cumulative exposure to 1800mg (days)	*1800mg single dose n=81*	*1200mg + 600mg n=79*	*Total*
≥1	79	79	158
≥2	73	53*	126
≥3	71	44*	115
≥4	70	35*	105
≥7	65	18*	83
14	55	5	60

*Note: the exposure to 1800mg in the flexible dosing group was not counted over consecutive days of exposure, but the total number of days exposed.

As shown in the table 60 subjects were exposed for 2 weeks and 83 were exposed for 1 week at 1800mg level.

4. Efficacy results





5. Safety results

(1) Serious events

There were no reports of death. Serious events were reported by 4 subjects, one in each treatment group.

Age gender	*Treatment*	*Adverse events*	*Investigator's assessment of causal relationship*
66 F	Oxaprozin K^+ 1800mg first 2 doses	Intractable vomiting leading to hospitalization, diagnosed with gallstone and cholelithiasis and had cholecystectomy, duodenal ulcer and gastritis by endoscopy	Vomiting: uncertain; Cholelithiasis: unlikely; Duodenal ulcer and gastritis: uncertain
62 F	Oxaprozin K^+ 1200mg for 1 day & 1800mg for 13 days	Infection related to post root canal procedure leading to hospitalization	Unlikely
61 F	Ibuprofen 400mg for 2 days	Symptomatic renal calculus leading to emergency room visit	Unlikely
91 M	Placebo	Hospitalized for abdominal pain and vomiting	No opinion

(2) Adverse events associated with overdosage

Ten subjects in the oxaprozin potassium 1200mg to 1800mg group took 2400mg within a 24-hour period (two additional 600mg doses plus the 1200mg daily dose on the same calendar day). Adverse events (AE) included 2 cases of rash, 1 case of nausea, 1 case of diarrhea, and 1 case of edema. The other 6 subjects had no AEs reported.

(3) Incidence of adverse events

Adverse events were reported in 44 of 79 (56%) patients on oxaprozin potassium 1800mg, 77 of 167 (46%) on oxaprozin potassium 1200-1800mg, 23 of 82 (28%) on ibuprofen 400mg, and 48 of 159 (30%) on placebo. Specific AEs reported by at least 3% of subjects in any treatment group were summarized in the table below in terms of the type of events, the number of subjects with at least one report of the event, the severity of the event for the moderate and severe categories (designated as M/S in the table, on a scale of mild, moderate, and severe), and the attribution of the event for those classified as uncertain or probably related to the study drug (designated as U/P in the table, based on the individual investigator's assessment). Also included in the table were melena, duodenal ulcer, and gastritis (not up to 3% incidence but considered clinically significant findings). AEs most frequently (≥5% of subjects) reported were nausea, dyspepsia, abdominal pain, diarrhea, headache, and vomiting. Subjects on oxaprozin potassium had dramatically higher (also statistically significant) AE incidence in GI symptoms especially upper GI distress symptoms than subjects on ibuprofen or placebo. One case of melena was reported in the oxaprozin potassium flexible dosing group. One case of symptomatic duodenal ulcer and gastritis (concurrently with gallstone and cholelithiasis) was reported in a subject on oxaprozin potassium 1800mg.

Table. Adverse events (≥3%) in study 022

	OxK 1800			*OxK 1200-1800*			*Ibuprofen 400*			*Placebo*		
Subjects treated	*N=79*			*N=167*			*N=82*			*N=159*		
Adverse events	*N (%)*	*M/S*	*U/P*	*N (%)*	*M/S*	*U/P*	*N (%)*	*M/S*	*U/P*	*N (%)*	*M/S*	*U/P*
Any adv event	**44(56)**	**22/4**	**15/23**	**77(46)**	**25/8**	**31/26**	**23(28)**	**7/4**	**12/4**	**48(30)**	**19/14**	**16/9**
Body as a whole	**7 (9)**	**4/0**	**1/3**	**11 (7)**	**3/0**	**4/1**	**4 (5)**	**1/0**	**2/0**	**10 (6)**	**5/3**	**5/0**
Chest pain	2 (3)	2/0	0/1	0			0			1 (<1)	1/0	1/0
Pain	1 (1)	0/0	0/0	0			1 (1)	0/0	0/0	4 (3)	2/1	2/0
Nervous system	**8 (10)**	**3/1**	**4/1**	**7 (4)**	**1/1**	**3/0**	**3 (4)**	**0/1**	**2/0**	**19(12)**	**7/6**	**3/6**
Headache	7 (9)	2/1	3/1	5 (3)	0/1	2/0	2 (2)	0/1	1/0	13 (8)	4/4	3/3
Dizziness	1 (1)	0/0	1/0	0			0			4 (3)	1/1	1/3
Digestive system	**38(48)**	**18/4**	**13/20**	**48(29)**	**18/5**	**19/23**	**9 (11)**	**1/1**	**4/4**	**9 (6)**	**4/2**	**6/1**
Abdominal pain	9 (11)	4/2	1/7	15 (9)	7/1	3/11	1 (1)	1/0	0/1	1 (<1)	0/1	1/0
Nausea	18(23)	8/1	5/12	15 (9)	4/1	6/7	3 (4)	0/1	1/2	2 (1)	0/0	1/0
Dyspepsia	10(13)	4/2	3/6	10 (6)	2/1	4/6	2 (2)	1/0	1/1	1 (<1)	1/0	1/0
Constipation	2 (3)	1/0	1/0	6 (4)	2/0	2/2	1 (1)	0/0	0/0	2 (1)	1/0	2/0
Diarrhea	8 (10)	2/0	5/1	5 (3)	4/0	2/1	2 (2)	0/0	2/0	4 (3)	2/1	2/1
Vomiting	4 (5)	3/1	1/3	4 (2)	3/1	1/1	0			1 (<1)	0/1	1/0
GE reflux	0			3 (2)	1/0	2/1	3 (4)	2/0	0/3	0		
Melena	0			1 (<1)	0/0	0/1	0			0		
Duodenal ulcer	1 (1)	1/0	1/0	0			0			0		
Gastritis	1 (1)	0/0	1/0	0			0			0		
Metabolic & nutritional	**2 (3)**	**1/0**	**0/2**	**1 (<1)**	**0/0**	**1/0**	**0**			**1 (<1)**	**0/0**	**0/0**
NPN increased	2 (3)	1/0	0/2	1 (<1)	0/0	1/0	0			0		
Psychiatric	**3 (4)**	**2/0**	**2/1**	**8 (5)**	**2/1**	**5/0**	**1 (1)**	**0/0**	**0/0**	**2 (1)**	**0/0**	**2/0**
Somnolence	3 (4)	2/0	2/1	5 (3)	1/1	3/0	0			1 (<1)	0/0	1/0
Skin & appendages	**3 (4)**	**1/0**	**2/1**	**8 (5)**	**2**	**4/2**	**2 (2)**	**1/0**	**0/0**	**6 (4)**	**2/1**	**0/3**
Rash	3 (4)	1/0	2/1	3 (2)	1/0	3/0	0			2 (1)	1/0	0/2

(4) Abnormal laboratory findings

Statistically significant mean changes in lab values in comparison with baseline were found in terms of decreased hemoglobin in all 3 active treatment groups and increased BUN, creatinine, AST, and ALT in the oxaprozin potassium treatment groups. The magnitude of the changes in group means was not considered clinically significant.

(5) Early terminations due to adverse events

A total of 42 patients discontinued early due to adverse events: 11 (14%) on oxaprozin potassium 1800mg, 16 (10%) on oxaprozin potassium 1200 to 1800mg, 3 (4%) on ibuprofen, and 12 (8%) on placebo. Upper GI distress symptoms (abdominal pain, nausea, dyspepsia, and vomiting) were the most frequently reported AEs resulting in the early terminations in subjects treated with oxaprozin potassium as shown in the table below (only the AEs that resulted in ≥3% discontinuations were shown).

AE causing withdrawal	*OxK 1800 N=79*	*OxK 1200-1800 N=167*	*Ibuprofen 400 N=82*	*Placebo N=159*
Any adv event	11 (14)	16 (10)	3 (4)	12 (8)
Abdominal pain	3 (4)	5 (3)	1 (1)	0
Nausea	2 (3)	5 (3)	1 (1)	0
Dyspepsia	2 (3)	1 (<1)	1 (1)	0
Vomiting	2 (3)	1 (<1)	0	0

(6) Other safety findings

The attempt to analyze drug-demographic interactions was limited by the small sample size and low event rates. Drug-disease interactions and drug-drug interactions were not studied.

6. Review of financial disclosure

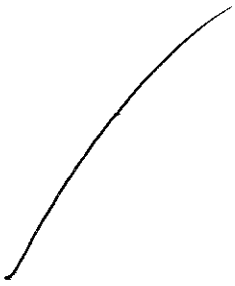
The sponsor submitted the financial disclosure form, FDA 3454, which certifies that no financial arrangements with the listed clinical investigators and subinvestigators at 24 study sites have been made where outcomes affect the value of compensation and that all the investigators and subinvestigators except one have no proprietary, significant equity interest, or any significant payments of other sorts as defined in 21 CFR 54.2(f).

One principal investigator owned common stock of the company and the steps taken to minimize the potential for bias were randomization, blinding, and following the standard operating procedures for the site monitoring and auditing.

The information on financial disclosure appears to be adequate to ensure that the reliability of the clinical data is not affected by financial interests.

7. Discussion

(1) Efficacy



(2) Safety

Exposure to 1800mg of oxaprozin potassium ranged from a single-dose exposure in 158 subjects (about half from each group) to a 14-day exposure in 60 subjects. Patients in the oxaprozin potassium groups had dramatically higher incidence of GI symptoms, especially upper GI distress symptoms, and higher rates of early terminations due to the upper GI distress symptoms than the ibuprofen or placebo group. There was also a case of symptomatic (vomiting) duodenal ulcer and

gastritis and a case of melena both in the oxaprozin potassium groups. Oxaprozin potassium at 1800mg or in the range of 1200 to 1800mg appeared to have an unfavorable GI safety profile in comparison to the control groups.

8. Conclusion

. Safety data were based on very limited exposure to the flexible dosing or 1800mg dosing: 60 subjects for 2 weeks. Dose-related GI toxicities (marked increase in upper GI distress symptoms, symptomatic ulcer and gastritis, GI bleeds as demonstrated in the study) could be a particular safety concern.

III. ADDITIONAL STUDIES OF OXAPROZIN POTASSIUM

(NDA volume 2 and 3, safety updates S4 submitted on 3/23/00, IND 47340-074)

There have been a number of studies of oxaprozin potassium conducted in addition to the 2-week OA study since the submission of the original NDA in May 1997, including 3 single-dose studies of 1200mg dose, one of which was a study of migraine and 2 were dental pain; one short-term multiple and flexible-dose study of 1200mg to 1800mg in patients with low back pain; 2 multiple-dose, 6-week studies of 1200mg dose in patients with osteoarthritis, one of which had an open-label extension phase of up to 24 weeks.

1. Single-dose dental pain studies of oxaprozin potassium 1200mg

(Studies 018, 020, 021)

The 2 dental studies were of similar design as the dental studies submitted in the original NDA. The active control in both studies was the combination product of oxycodone hydrochloride 5mg and acetaminophen 500mg. The results confirmed the findings from the dental study 007 (refer to the medical review of the original NDA) that a single 1200mg dose could only provide 24-hour pain relief in 1/3 or less of the study population (i.e. the proportion not requesting rescue medication within 24 hours after the initial dose) and the median time to rescue medication was between 7 and 8 hours.

2. One-week study of low back pain at 1200mg to 1800mg

(Study 019)

This study is presented in detail because it provides valuable information about the flexible dosing at 1200mg to 1800mg.

(1) Protocol

Design: It was a multiple-dose, randomized, double-blind, placebo-controlled, parallel study of oxaprozin potassium 1200mg to 1800mg conducted at 20 centers in 225 patients with acute low back pain.

Sample population: Eligible subjects were adult patients with an acute episode or an acute exacerbation of intermittent low back pain (pain free for at least 3 months

prior to present episode) of 1 to 6 days in duration prior to enrollment and baseline pain intensity of ≥50mm on a 100mm VAS scale.

Treatment: Patients were randomized to one of the two treatment groups to receive oxaprozin potassium 1200mg every morning for 7 days and an additional dose of 600mg taken as needed 6 hours after the morning dose during the first 3 days, or the matching placebo. Tylenol up to 3000mg a day was allowed as rescue medication but not to be taken within 6 hours prior to daily dosing with 1200mg of oxaprozin potassium.

Data collection: Patients were instructed to record in a daily diary their present PI and their average PI in last 24 hours (recording time with respect to dose was not specified for days 2 to 7) and complete the Activity Tolerance Survey daily at bedtime, the Roland Disability Index and SF-8 Health Survey on days 1, 4 and 8, and Patient's Global Evaluation on days 4 and 8. Physicians were to assess the Maximum Forward Lumbar Flexion (fingertips-to-floor method) on days 1, 4 and 8 and provide Global Evaluation on days 4 and 8.

Efficacy:

Safety: Safety was monitored by reporting treatment emergent AEs and changes in vital signs and physical examinations.

(2) Demographic and other baseline characteristics

The study population consisted of 225 subjects who were randomized to the 2 treatment arms, with an age range of 18 to 76 years and a mean around 40 years, 76% Caucasian and 52% females. There were no statistically significant treatment group differences with regard to demographic characteristics such as age, gender, race, height, and weight, with regard to baseline vital signs, and with regard to the baseline disease status, except that subjects in the oxaprozin potassium 1200mg to

1800mg group had significantly worse scores in 1 of the 8 domains - the physical functioning domain of the SF-8 Health Survey than placebo subjects.

(3) Study execution and drug exposure

Of 225 subjects randomized 17 were enrolled with violation of eligibility criteria, including ALT/AST elevation at baseline in 11 subjects, less severe baseline PI in 2, no baseline pain/disability data in 1, history of nasal polyps in 1, longer than allowed duration of the current pain episode in 1, and underweight in 1 (no information on treatment group comparison with respect to the type of protocol violation was provided).

The reasons for early termination per treatment group were summarized in the table below:

Reasons for the early termination from the study	***Oxaprozin K^+ 1200-1800mg n=113***	***Placebo n=112***
Lack of efficacy	4 (4%)	12 (11%)
Lost to follow up	1 (<1%)	3 (3%)
Protocol violation	12 (11%)	5 (4%)
Non-compliance	2 (2%)	3 (3%)
Adverse events	3 (3%)	2 (2%)
Total	22 (19%)	25 (22%)

There were 74 subjects exposed to the additional 600mg dose (equivalent to 1800mg a day) on one of the first 3 days and 21 on all 3 days.

(4) Efficacy results

(5) Safety results

Serious events: There were no reports of death and only one serious event: a case of cellulitis leading to hospitalization in a placebo patient.

Incidence of adverse events: Adverse events (AE) were reported in 46 of 113 (41%) patients on oxaprozin potassium 1200-1800mg and 33 of 111 (30%) on placebo. Specific AEs reported by at least 3% of subjects in any treatment group were summarized in the table below in terms of the type of events, the number of subjects with at least one report of the event, the severity of the event for the moderate and severe categories (designated as Mod/Sev in the table, on a scale of mild, moderate, and severe), and the attribution of the event for those classified as uncertain or probably related to the study drug (designated as Unc/Pro in the table, based on the individual investigator's assessment). AEs most frequently (≥5% of subjects) reported were nausea, dyspepsia, abdominal pain, diarrhea, and headache. Subjects on oxaprozin potassium had dramatically higher AE incidence in GI symptoms especially upper GI distress symptoms than subjects on placebo.

	Oxaprozin K 1200-1800mg			***Placebo***		
Subjects treated	***N=113***			***N=111***		
Adverse events	***N (%)***	***Mod/Sev***	***Unc/Pro***	***N (%)***	***Mod/Sev***	***Unc/Pro***
Any adverse event	**46 (41)**	**11/8**	**31/26**	**33 (30)**	**21/3**	**16/9**
Nervous system	**7 (6)**	**2/4**	**6/0**	**16 (14)**	**11/0**	**10/2**
Headache	4 (4)	1/3	3/0	11 (10)	8/0	7/1
Dizziness	1 (<1)	0/0	1/0	3 (3)	2/0	2/1
Digestive system	**35 (31)**	**10/4**	**16/16**	**11 (10)**	**6/1**	**4/6**
Nausea	13 (12)	5/1	6/7	3 (3)	0/3	2/1
Dyspepsia	10 (9)	4/0	2/7	2 (2)	0/2	1/1
Abdominal pain	9 (8)	4/1	4/5	3 (3)	1/3	1/2
Diarrhea	4 (4)	0/1	4/0	5 (5)	0/5	1/4
Flatulence	4 (4)	0/2	2/2	0		
Psychiatric	**9 (8)**	**2/1**	**3/4**	**5 (5)**	**3/0**	**4/1**
Nervousness	3 (3)	0/0	2/0	0		

Early terminations due to adverse events: There were 5 patients discontinued early due to adverse events: 3 on oxaprozin potassium 1200 to 1800mg (due to abdominal pain, headache, and migraine, respectively) and 2 on placebo (due to diarrhea and rash, respectively).

3. Six-week osteoarthritis studies of oxaprozin potassium 1200mg
(Studies 014 and 015)

Safety data from study 014 were submitted previously as safety updates to the original NDA and discussed in the original medical review dated May 20, 1998. The details will not be repeated here. Study 015 had an identical design as study 014, specifically, a multiple-dose, 6-week, double-blind, randomized, active- and placebo-controlled, parallel study of oxaprozin potassium 1200mg in patients with OA.

A total of 377 patients were treated: 126 with oxaprozin potassium 1200mg a day, 126 with etodolac 400mg twice a day, and 125 with matching placebo. There were no statistically significant differences among the treatment groups with regard to demographic characteristics such as gender and race (but age was 2 years older in the placebo group and 2 years younger in the etodolac group as compared to the oxaprozin potassium group), baseline vital signs, or baseline disease status.

The number and percentage of patients exposed to the test drugs are summarized in the table below:

Cumulative exposure (weeks)	*Oxaprozin K^+ 1200mg n=126*	*Etodolac n=126*	*Placebo n=125*
<2	126 (100%)	126 (100%)	125 (100%)
≥2	124 (98%)	124 (98%)	119 (94%)
6	103 (82%)	107 (84%)	91 (72%)

Serious events: No deaths were reported. There were 7 serious events: 2 cases of cancer, 3 cases of coronary artery obstruction, 1 case of hip fracture, and 1 case of hospitalization for elective bladder resuspension. None was considered study drug-related.

Incidence of Adverse events (AEs): AEs were reported in 51% patients on oxaprozin potassium, 35% on etodolac, and 26% on placebo. AEs reported by at

least 3% of subjects in any treatment group were summarized in the table below. The most frequently (≥5 % of subjects) reported were dyspepsia, abdominal pain, BUN increased, and headache. Incidence of GI symptoms in general and dyspepsia and abdominal pain in particular was much higher in the oxaprozin potassium group than in the etodolac or placebo group. There was one case of melena (details not provided) reported in the oxaprozin potassium group.

Adverse event	*Oxaprozin K^+ 1200mg N (%)*	*Etodolac N (%)*	*Placebo N (%)*
Digestive system	24 (19)	10 (8)	9 (7)
Dyspepsia	8 (6)	3 (2)	1 (<1)
Abdominal pain	6 (5)	2 (2)	4 (3)
Nausea	5 (4)	3 (2)	4 (3)
BUN increased	6 (5)	1 (<1)	0
Headache	5 (4)	7 (6)	4 (3)
Rhinitis	5 (4)	3 (2)	1 (<1)

Early termination due to adverse events: A total of 27 patients were discontinued early due to adverse events: 13 (10%) on oxaprozin potassium, 9 (7%) on etodolac, and 5 (4%) on placebo, remarkably more patients terminated due to abdominal pain and vomiting in the oxaprozin potassium group than either the etodolac or placebo group.

4. Open-label, 24-week extension of osteoarthritis study

Study 017 was an open-label, 24-week extension of osteoarthritis study 015 conducted at 21 centers. Of 189 subjects who received at least one dose of study medication (medication to be taken with the evening meal) 123 (65%) completed 24 weeks of treatment. The cumulative exposure is summarized in the table:

Cumulative exposure to 1200mg (weeks)	*<2*	*≥2*	*≥6*	*≥12*	*≥18*	*24*
N (%)	189 (100)	185 (98)	175 (93)	161 (85)	136 (72)	123 (65)

Serious events: No deaths were reported. There were 8 patients who were reported as having serious events: 1 case of bronchospasm, 1 case of

pyelonephritis, 1 case of basal cell carcinoma, 2 cases of myocardial infarction, 1 case of diverticulitis, 1 case of sepsis, and 1 case of stroke.

Incidence of Adverse events (AEs): AEs were reported in 106 (56%) patients. The most frequently reported were dyspepsia (7%); arthralgia, leg cramps (5%); back pain, peripheral edema, headache, rhinitis (4%); abdominal pain, anemia, constipation, creatinine increased, rash, AST increased, ALT increased, sinusitis (3%).

Early termination due to adverse events: A total of 31 (16%) patients were discontinued early due to adverse events mostly due to GI symptoms (10 cases, or 5%) including abdominal pain (4 cases, or 2%), dyspepsia (3 cases, or 2%), nausea (1 case), diverticulitis (1 case), and constipation (1 case). The other AEs leading to early terminations thought to be drug-related were rash, ALT increase, and pruritus.

IV. LABELING REVIEW

1. Labeling recommendations

(2) Drug interaction with ACE-inhibitors
(IND

Study 026 was a small (n=29, 19 evaluable subjects) PK study of oxaprozin acid at 1200mg, which was not adequately designed (not randomized or double blind) or well-controlled (no control groups). The clinical findings in terms of the changes in group mean blood pressure were very difficult to interpret due to multiple confounding factors such as the severity of hypertension, the dose level of enalapril (3 doses were allowed: 10mg, 20mg, and 40mg), the concomitant medication that may have an effect on the patient's blood pressure, etc. The individual response varied from decreased supine diastolic pressures in 8 of 19 subjects to increased ones in 11 of 19 subjects when blood pressures were compared between post- and pre-coadministration with oxaprozin. The remarkable PK findings were included.

(3) Drug interaction with lithium
Plasma level monitoring is recommended for subjects on lithium treatment and lithium level monitoring should be increased when lithium is coadministered with NSAIDs.

(4) Geriatric use
Statistically significant differences between the age groups were shown in some individual AEs in the 24-week OA study. Since the study was not designed to investigate drug tolerance with respect to age, no difference in the total number of subjects reporting AEs does not necessarily translate to equal tolerance.

(5) Other modifications
Most of the other changes are for clarification purpose.

MEDICAL OFFICER REVIEW

NDA Number:	20-776
Drug Name:	Oxaprozin potassium 600mg tablet
Trade Name:	Benilas™
Sponsor:	G.D. Searle & Co. 4901 Searle Parkway Skokie, IL 60077 Winifred Begley (Director, Regulatory Affairs) Tel: 847-982-8155 Fax: 847-982-8090
Date submitted	May 19, 1997
Date Received at FDA:	May 20, 1997
Medical Reviewer:	Christina Fang, M.D.
Secondary Reviewer:	John Hyde, M.D., Ph.D.
Drug Class:	NSAID
CSO Contact:	Victoria Lutwak

Christina Fang 5/20/98 — Christina Fang, M.D. Date

JEH 5-20-98 — Team Leader Date

CC: Original NDA 20-776
HFD-550/Division File
HFD-550/C. Fang/V. Lutwak/C. Yaciw/W. Coulter/A. Noory
HFD-340
R/D Init. by:
F/T by:

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I. INVENTORY OF CLINICAL STUDIES

INVENTORY OF CLINICAL TRIALS (See Appendix A for abbreviation)

Protocol # Investigator/Site	*Drug (mg)*	*Subj (N)*	*Outcome summary*	*Comment*
Dental Pain Studies: single-dose, double-blind (single-blind for study 004), randomized, placebo-controlled, parallel, single-center (2 centers for study 010)				
	OxK-1200	50		
	OxK-900	51		
	OxK-600	51		
	OxK-300	50		
	Placebo	50		
	OxK-1200	58		Redosing with Ox-K-600 once at 6 hours was allowed.
	Ox-1200	55		
	Ibu-400	55		
	Placebo	56		
	OxK-1200	57		
	Ox-1200	56		
	Ibu-400	56		
	Placebo	56		
	OxK-1200	57		
	Ox-1200	56		
	Ibu-400	56		
	Placebo	56		
	OxK-1200	58		
	OxK/Ox-1200	56		
	Ox-1200	57		
	Ibu-400	56		
	Placebo	55		

Protocol # Investigator/Site	*Drug (mg)*	*Subj (N)*	*Outcome summary*	*Comment*
Osteoarthritis Study: multiple-dose, double-blind, randomized, parallel, placebo-controlled, thirty-centers				
	OxK-1200 Ox-1200 Placebo for 24 weeks	322 320 161	OxK-1200 appeared to be comparable to Ox-1200 in efficacy and safety for OA, except that OxK-1200 might lead to higher risks of upper GI ulcers.	There were 7 ulcer cases all reported in the OxK group; 6/7 were symptomatic & 1 had slight bleeding.
Osteoarthritis Study: multiple-dose, double-blind, randomized, parallel, placebo-controlled, multicenter				
	OxK-1200 Eto-400 BID Placebo for 6 weeks	124 127 127	Significantly more GI symptoms, nausea, SGPT↑, anemia, & withdrawals due to GI symptoms were reported for OxK than for Eto. There was 1 case of bleeding ulcer in the OxK group.	Data from 4-month safety update not submitted with the original NDA; and the study report is still not available.
Pharmacokinetic Studies: single-dose (multiple-dose for study 005), open, randomized, parallel (3-way crossover for study 008), single-center				
	OxK-1200 OxK/Ox-1200 Ox-1200	12 12 12	In comparison to Ox-1200, OxK-1200 showed higher C_{max}, shorter T_{max} and $T_{1/2}$ after a single dose.	
	OxK-1200 OxK/Ox-1200 Ox-1200 for 7 days	15 12 13	OxK-1200 and Ox-1200 were bioequivalent by comparing AUC, C_{max}, and C_{min} for the total concentration at steady states.	
	OxK-1800 OxK-1200 OxK-600	36 36 36	Lack of dose proportionality was demonstrated by the nonlinear variation pattern of AUC with the increase of doses.	
	OxK-1200	50	The 2 formulations of oxaprozin potassium: the formulation used in clinical trials and the formulation for commercial distribution were bioequivalent.	
	OxK-1200	48	There was no food effect on the maximum and total absorption. T_{max} was somewhat delayed by food.	

II. OVERALL SUMMARY

1. Background information

    (1) Introduction
    (2) Drug substance and drug product
    (3) Pharmacokinetics

2. Efficacy results

3. Safety results

    (1) Multiple-dose study of osteoarthritis in 24 weeks
    (2) Short term and single-dose studies
    (3) Multiple-dose study of osteoarthritis in 6 weeks
    (4) Safety of oxaprozin
    (5) Safety summary

4. Benefits and risks

5. Overall recommendations

6. Labeling recommendations

    (1) Indication
    (2) Precaution
    (3) Adverse reactions
    (4) The maximum dosage

1. Background information

(1) Introduction

Oxaprozin potassium is a potassium salt of oxaprozin acid (Daypro®), a nonsteroidal anti-inflammatory agent of the propionic acid chemical class. Daypro was approved for the management of signs and symptoms of rheumatoid arthritis and osteoarthritis in the United States in 1992. The recommended dosing is 1200mg once a day, or individualized minimum effective dose, but not to exceed 1800mg a day in divided doses. Daypro is not indicated for acute pain because of its lower solubility and longer T_{max}. The sponsor Searle has formulated the oxaprozin potassium salt with the expectation of a faster analgesic onset as a result of improved drug absorption in comparison to Daypro® while retaining the once-a-day dosing schedule.

(2) Drug substance and drug product

Oxaprozin potassium has a chemical name: 4,5-diphenyl-2-oxazolepropanoic acid, potassium salt; a molecular formula: $C_{18}H_{14}KNO_3$; and molecular weight of 331.40.

The drug substance is a white to off-white powder with a slightly bitter taste and no characteristic odor, has a melting point of 215°C, and is slightly soluble in alcohol and very soluble in water.

Each tablet of drug product contains 677.9mg of oxaprozin potassium, which is equivalent to 600mg of oxaprozin. The product is expected to be stable at room temperature (25°C) for —

(3) Pharmacokinetics

There were five pharmacokinetic (PK) studies:
a single-dose study in comparison of the salt and acid formulations (study 001);
a multiple-dose study in comparison of the salt and acid formulations (study 005);
a dose proportionality study of oxaprozin potassium (study 008);
a food effect study of oxaprozin potassium (study 013); and

a bioequivalence study in comparison of the commercial formulation and the formulation used in clinical trials (study 012).

In the single-dose PK study of the two formulations, a higher C_{max} (26% for total and 49% for free concentration) and a shorter T_{max} (33% for total and 4% for free concentration) and $T_{1/2}$ were shown when oxaprozin potassium was compared to oxaprozin based on the sponsor's analysis using geometric least squares means.

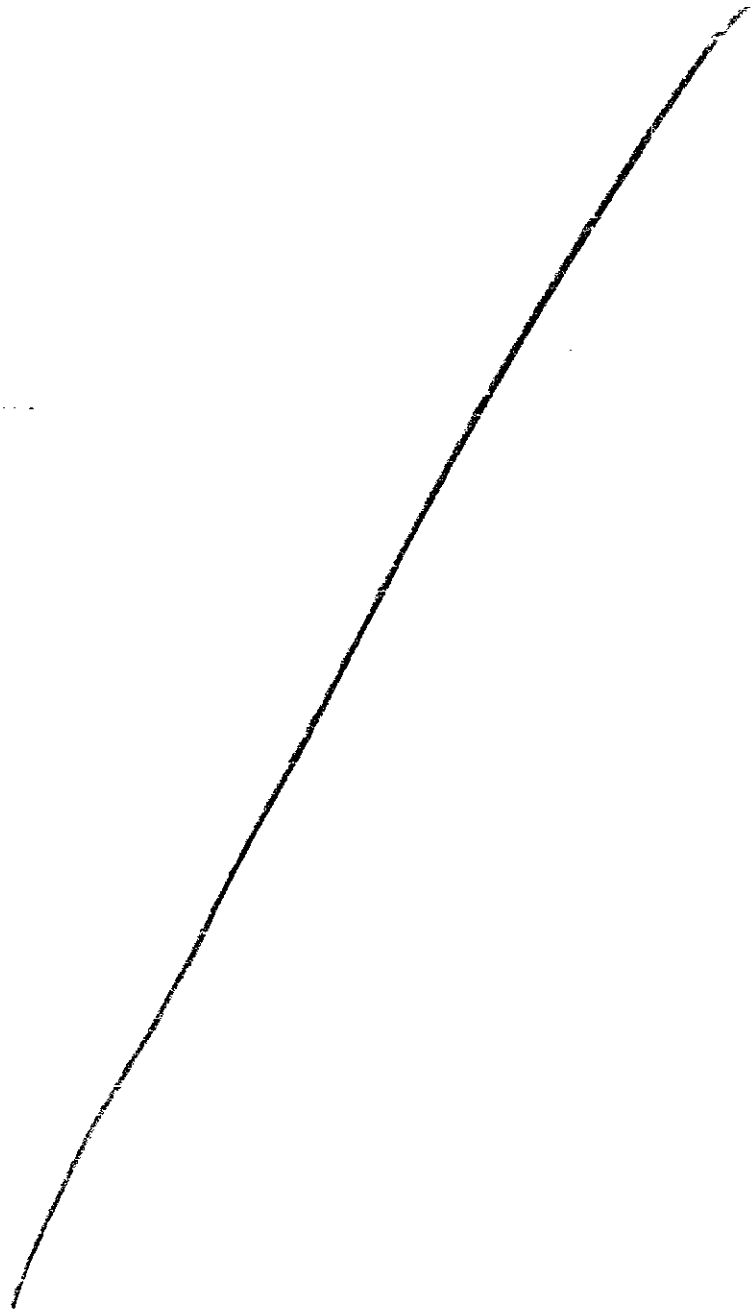
In the one-week repeated dose study, the salt and acid formulations were considered to be bioequivalent at steady states. The conclusion was based on the 90% confidence intervals for the ratio of AUC, C_{max}, and C_{min} falling in a range of 80 to 125% with respect to total concentration (but not to unbound concentration).

In the dose proportionality study using 600mg, 1200mg, and 1800mg of oxaprozin potassium, the lack of dose proportionality was demonstrated by less than proportional increases in total drug concentration and more than proportional increases in unbound concentration with the increase of doses. It was probably due to nonlinear protein binding.

Food did not alter the maximum and total absorption but delayed the time to reach the maximum concentration.

The commercial formulation appeared to be bioequivalent to the clinical trial formulation based on the weight-corrected calculations (see PK review for details).

2. Efficacy results



(2) Osteoarthritis

The 24-week osteoarthritis (OA) trial was a double-blind, randomized, parallel, placebo- and active treatment-controlled study of oxaprozin potassium conducted at thirty-centers. The study enrolled male and female adult subjects with a minimum of 6-month history of osteoarthritis and with OA symptoms at least moderate in severity at baseline. Patients were randomized at a 2:2:1 ratio to receive once daily doses of oxaprozin potassium 1200mg, oxaprozin 1200mg, or placebo for 24 weeks. The primary efficacy parameters were knee pain on weight-bearing, knee pain on motion, patient's global, and physician's global, assessed at baseline and weeks 2, 6, 12, and 24. Patients were also evaluated by using three health-related quality of life surveys.

A total of 803 patients, mostly elderly and Caucasians, received at least 1 dose of the study medication: 322 received oxaprozin potassium, 320 received oxaprozin, and 161 received placebo. About 50% patients had drug exposure for 24 weeks and two thirds for 12 weeks.

Oxaprozin potassium and oxaprozin performed statistically better than placebo in terms of patient's global, physician's global, knee pain on weight bearing, and knee pain on motion. The positive results were supported by the findings of the WOMAC assessment. The two active drugs were shown to be comparable in efficacy for the symptomatic relieve in OA based on Q-statistics analysis.

(3) Efficacy Summary

The OA trial revealed that oxaprozin potassium 1200mg once daily dosing had statistically better performance than placebo as measured by all 4 primary efficacy parameters and was comparable to oxaprozin in efficacy for OA.

Because the salt and acid formulations of oxaprozin were shown to be bioequivalent at steady states, efficacy data of Daypro for OA and RA indications are accepted as supporting evidence for oxaprozin potassium to be used for the same indications.

3. Safety results

(1) Multiple-dose study of 24 weeks in osteoarthritis

The study was briefly described in the efficacy section above. Out of 322 patients assigned to the oxaprozin potassium group, 183 (57%) completed the 24-week treatment period, very similar to the number and percentage (184 or 58%) of completers in the oxaprozin group.

There were significantly more adverse events (AEs) reported in patients on oxaprozin potassium and on oxaprozin than on placebo for the overall incidence, GI distress symptoms, and liver enzyme increases; and more early study terminations due to AEs, especially due to GI distress symptoms in patients on oxaprozin potassium than placebo. Six symptomatic ulcer and one bleeding ulcer were all reported in patients receiving oxaprozin potassium. Except serious GI events, most serious cases were not considered as study drug related. The results of subgroup analysis based on demographic characteristics such as age, gender, and race did not suggest increased risks of drug intolerance.

(2) Short term and single dose studies

In 9 single dose studies, 578 of 1450 subjects received oxaprozin potassium, of which 36 receive 1800mg and 426 received 1200mg. In the one-week multiple dose PK study, 15 of 30 were given oxaprozin potassium 1200mg.

The frequency of AE reports was much lower than what was recorded in the 24-week multiple dose study as expected. The most frequently reported were again GI symptoms. Serious events were not observed in these studies.

(3) Multiple-dose study of 6 weeks in osteoarthritis

The 6-week OA trial was a multiple-dose, double-blind, randomized, parallel, placebo-controlled study completed after the NDA submission. A total of 378 patients were treated: 124 with oxaprozin potassium 1200mg a day, 127 with etodolac 400mg twice a day, and 127 with placebo. There were no statistically significant differences among the treatment groups with regard to demographic

characteristics such as age, gender, and race. The number and percentage of patients exposed to the test drugs for more than 2 weeks were: 104 (84%) to oxaprozin potassium, 119 (94%) to etodolac, and 108 (85%) to placebo.

There were significantly more AEs reported in patients on oxaprozin potassium than on placebo in terms of the overall incidence, general GI symptoms especially upper GI distress symptoms, increase in SGOT, flu symptoms, and early study termination due to GI symptoms. Also, significantly more AEs were reported in patients on oxaprozin potassium than on etodolac in terms of general GI symptoms, nausea, increase in SGPT, anemia, and early termination due to GI symptoms. There was one case of bleeding ulcer in the oxaprozin potassium group. No statistically significant differences in terms of clinically meaningful lab abnormalities were found between the treatment groups. Neither were interactions between the adverse events and demographic characteristics such as age, gender, and race.

(4) Safety of oxaprozin (Daypro)

Since the market approval of Daypro, sixteen clinical trials have been conducted in 1280 patients, of whom of 699 received oxaprozin ranging from a single dose up to 1800mg, to daily doses of 1200mg up to 8 weeks or 1800mg up to 4 weeks. Most frequently reported AEs in the oxaprozin group were GI symptoms such as abdominal pain, dyspepsia, nausea, diarrhea, constipation, flatulence, and melena. The remarkable findings included one case of gastric ulcer, 5 cases of melena (gross bleeding), 2 cases of elevated SGOT and SGPT and 8 cases of abnormal hepatic function. Patients on 1800mg (in 3 divided doses) appeared to have more reports of upper GI distress symptoms, suggesting a dose-response relationship.

Based on the sponsor's estimate, oxaprozin was distributed to — people in the first 4 years following the market approval. The sponsor received reports of 2597 adverse events, of which 448 were categorized as serious. The most frequently reported and remarkable events were upper GI distress symptoms such as dyspepsia, nausea, and abdominal pain, GI hemorrhage, allergic and skin reactions. The reporting frequency on fatal events based on all the adverse events reported for oxaprozin was less than 2%.

The literature reports on the adverse events associated with oxaprozin consisted mainly GI, especially upper GI distress symptoms at lower reporting frequencies than what occurred in the sponsor conducted trials.

(5) Safety summary

In the clinical trials designed to study oxaprozin potassium, a total of 2599 subjects received at least one dose of study medication to date, including 1039 received oxaprozin potassium, 80 received oxaprozin potassium/oxaprozin bilayer tablet, 569 received oxaprozin, 223 received ibuprofen, 127 received etodolac, and 561 received placebo. The exposure to oxaprozin potassium ranged from a single dose up to 1800mg (36 subjects) to multiple doses of 1200mg for 24 weeks (187 OA patients). A total of 56 subjects were exposed to 1800mg daily dosing: 36 received a single dose in a PK study and 20 received 1200mg dose followed by a 600mg dose in a single-dose analgesic study.

The most frequent and remarkable adverse events associated with oxaprozin potassium were upper GI distress symptoms. There were 2 hemorrhagic ulcer and 6 symptomatic ulcer, all reported in the oxaprozin potassium group, suggesting an increased GI risk associated with the salt formulation of oxaprozin.

Based on the post-approval clinical studies, spontaneous AE reports, and literature reports, there were no dramatic changes in the safety profile of oxaprozin acid.

4. Benefits and risks

Oxaprozin potassium 1200mg on a once daily dosing schedule is effective for symptomatic treatment of osteoarthritis as demonstrated by the six-month OA study, where oxaprozin potassium was shown to be comparable to oxaprozin in efficacy and safety in general. Since the acid and salt formulations of oxaprozin were bioequivalent at steady states, a cross reference to the efficacy of Daypro in the symptomatic treatments of both osteoarthritis and rheumatoid arthritis is acceptable.

Oxaprozin potassium is considered reasonably safe and its safe profile was not dramatically different from that of NSAID class. However, oxaprozin potassium does not appear to have added advantage to oxaprozin acid. The increased solubility of the salt formulation did not help to improve the analgesic onset as expected but lead to a greater risk for GI ulcers and ulcer complications.

Elderly and the other demographically divided subgroups were not shown to have increased risk for adverse events based on the six-month OA study in more than 300 patients per active treatment arm.

In summary, oxaprozin potassium 1200mg to be taken once daily is considered effective and safe for relief of signs and symptoms of osteoarthritis and rheumatoid arthritis,

5. Overall recommendations

Oxaprozin potassium 1200mg once daily for management of signs and symptoms of osteoarthritis and rheumatoid arthritis is recommended for approval based on the results of OA study and bioequivalence study. The maximum daily dose should be limited to 1200mg because of the greater ulcerogenic potential of oxaprozin potassium at 1200mg level and the lack of safety information with regard to the use of 1800mg per day in divided doses.

6. Labeling recommendations

The recommended major revisions to the labeling and the reasons for the changes can be found in the section VI of the review and will be highlighted here.

(1) Indication

All the labeling statements about the use of the drug for — should be deleted.

(2) Precaution

The NSAID labeling statements about close monitoring of patients with significant renal impairment should be inserted.

The statements about the platelet-aggregation and bleeding time based on the findings of a small open-label study should be deleted.

The statements about the drug interactions with methotrexate, warfarin, and glyburide should be revised to reflect the changes based on Dr. Widmark's review of the recent labeling supplement for Daypro.

(3) Adverse reactions

The NSAID class labeling template statements should be used with the adjustment to reflect the experience of the individual drug.

(4) The maximum dosage

The maximum total daily dosage should not exceed 1200mg —

III. – EFFICACY REVIEW

15 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

IV. OSTEOARTHRITIS

THE REVIEW OF OSTEOARTHRITIS STUDY

1. Study design

2. Execution

3. Efficacy results

4. Safety results

    (1) Drug exposure
    (2) Incidence of adverse events
    (3) Serious adverse events
    (4) Early terminations due to adverse events
    (5) Gastrointestinal adverse events
    (6) Abnormal laboratory findings
    (7) Adverse events with respect to demographic characteristics

5. Summary

6. Conclusion

7. Recommendations

8. Tables

MULTIPLE-DOSE STUDY IN PATIENTS WITH OSTEOARTHRITIS
(NDA volumes 1.40-1.47)

1. Study design

This was a double-blind, randomized, parallel, placebo- and active treatment-controlled study of oxaprozin potassium conducted at thirty-centers. The key features of the protocol were presented in the table below:

Study population	Male and female adult subjects with a minimum of 6-month history of osteoarthritis of the knee and with at least moderate baseline OA symptoms (defined by scores ≥ 2 on a 0-4 categorical scale in terms of patient's global, physician's global, and knee pain on weight-bearing or on motion), who had a Functional Capacity Classification of I-III.
Treatment and dosing	Oxaprozin potassium 1200mg, oxaprozin 1200mg, or placebo once a day for 24 weeks.
Efficacy assessment	Joint pain and function primarily: knee pain on weight-bearing, knee pain on motion, patient's global, and physician's global at baseline and weeks 2, 6, 12, and 24; and QOL secondarily: SF-36 Health Survey, WOMAC Health Status, and MOS Pain Survey at baseline and weeks 2, 6, and 24.
Safety assessment	Spontaneous report of adverse events (AE); routine laboratory tests (CBC, chemistry, and urinalysis) at baseline and weeks 2, 6, 12, 18, and 24; and physical exam at baseline and weeks 6 and 24.

Note: QOL stands for quality of life; SF-36 for Short Form-36; WOMAC for the Western Ontario MacMaster Arthritis Center; and MOS for the Medical Outcome Studies.

2. Execution

There was a total of 803 subjects who were treated: 322 with oxaprozin potassium 1200mg, 320 with oxaprozin 1200mg, and 161 with placebo. The subjects were males and females (about 70% females) age 22 to 87 (majority of whom were older than 40 (≥93%), mean age at early sixties) and were mostly Caucasians (82.9%). There were no statistically significant differences among the treatment groups with regard to demographic characteristics such as age, gender, race, and height (except weight that the mean weight of the oxaprozin potassium group was significantly (5 kg) less than the placebo group), and with regard to the mean duration of disease (9.3 years), baseline OA status, baseline health-related quality of life assessment, and baseline vital signs. About 50% subjects completed the 24-week study: 57% in the oxaprozin potassium group, 58% in the oxaprozin group, and 48% in the placebo group. The early terminations were mostly due to adverse events and treatment failures. The reasons are summarized in Table 1 at the end of the section. The extent of drug exposure is summarized in Table 2. The mean compliance in taking study medication was 96% or higher and was not significantly different between the treatment groups.

Drug (mg)	*Subj (N)*	*Age (yr) Mean(range)*	*Sex (N) M / F*	*Race (N) C/B/A/H/O*	*Height Mean (range)*	*Weight Mean (range)*
OxK-1200	322	61 (22-86)	93/229	271/37/0/13/1	166 (145-193)	87 (50-162)
Ox-1200	320	60 (23-87)	103/217	266/39/0/15/0	168 (138-201)	90 (47-172)
Placebo	161	60 (24-83)	55/106	129/24/1/7/0	168 (146-196)	92 (48-155)

3. Efficacy results

The remarkable statistically significant differences between the treatment groups, in terms of the mean changes from baseline for each of the primary efficacy parameters, are presented in the table below, where the statistically significant differences were obtained by applying Protected Fisher's LSD tests at the 0.05 level. The tables with details can be found on pages VII-27 to 30 in Appendix A.

Primary efficacy parameters	***Patient's global***	***Physician's global***	***Knee pain on weight bearing***	***Knee pain on motion***
Statistically significant differences in changes from baseline at scheduled visits (weeks 2, 6, 12, and 24)				
OxK-1200 > Placebo	2, 6, 12	2, 6, 12, 24	2, 6, 12	2, 6, 12, 24
Ox-1200 > Placebo	2, 6, 12	2, 6, 12, 24	2, 6, 12	2, 6, 12, 24
OxK-1200>Ox-1200	6			

- Statistically significant differences were shown in favor of oxaprozin potassium 1200mg and oxaprozin 1200mg over placebo for all of the primary efficacy parameters at the week 2, 6, and 12-week visits and for two of the four primary efficacy parameters: physician's global and knee pain on motion at the last (24-week) visit.

- Statistically significant differences between oxaprozin potassium 1200mg and oxaprozin 1200mg were not shown for any of the 4 primary efficacy parameters. Oxaprozin potassium 1200mg was shown to be comparable to oxaprozin 1200mg for the symptomatic relief for OA based on the analysis using Q-statistics: $0.8<Q<1.2$ and $0.6<Q_L$ (see page VII-31 in Appendix A for details).

The results of the three health related quality of life assessments are summarized in Tables 3 to 5 at the end of the section (see page VII-32 to 45 of Appendix A for details). The statistically significant differences in favor of the active treatments over placebo were shown consistently over time only by the WOMAC assessment.

4. Safety results

(1) Drug exposure

More than 50% of subjects were exposed to oxaprozin potassium and oxaprozin for 24 weeks and about two thirds were exposed for at least 12 weeks as shown in Table 2.

(2) Incidence of adverse events

Adverse events (AE) were reported in 82% patients on oxaprozin potassium, 76% on oxaprozin, and 66% on placebo. They are summarized in Appendix B (pages VIII-3 to 11), in terms of the type of events (coded by COSTART terms and classified by 12 body systems), the number of subjects who had at least one report of the event, had the event reported as severe (on a scale of mild, moderate, and severe), and had the event thought to be study drug-related (based on the individual investigator's assessment). AE's most frequently (≥5 % of subjects) reported were dyspepsia, nausea, pharyngitis, abdominal pain, headache, diarrhea, constipation, flu syndrome, SGOT increased, flatulence, SGPT increased, cough increased, and arthralgia as shown in Table 6. Both active treatment groups had statistically significantly more AE's than the placebo group in terms of the overall incidence, and particularly, in terms of the GI distress symptoms and the increases in liver enzymes.

(3) Serious adverse events

There were three reports of death: one in each treatment group. The first case was a 71 year-old female with a history of hypertension and hypothyroidism who presented at emergency room with shortness of breath and vaginal bleeding after being on oxaprozin potassium for 6 weeks. After a set of routine diagnostic tests with negative findings, she was discharged home, but then had full cardiac arrest the next day.

The second case was a 73 year-old female with a history of hypertension and angina who was admitted to the hospital for pulmonary edema and respiratory insufficiency after being on oxaprozin for 11 weeks. She experienced progressive respiratory failure and expired a week later.

The third case was a 56 year old male placebo patient with a history of heart disease who developed acute myocardial infarction and expired.

Other serious events were listed in Table 7 by the treatment groups. Except the gastrointestinal ulcer cases, most of these serious events were not considered as study drug related by the investigators.

(4) Early terminations due to adverse events

A total of 161 patients discontinued early due to adverse events: 80 (25%) on oxaprozin potassium, 61 (19%) on oxaprozin, and 20 (12%) on placebo, significantly more on oxaprozin potassium than on placebo. The most frequent AEs (≥3% in at least one treatment group) leading to discontinuation were nausea, abdominal pain, and dyspepsia (12, 10, and 9 cases in the oxaprozin potassium group and 9, 7, and 8 cases in the oxaprozin group, respectively).

(5) Gastrointestinal adverse events

There were 7 (2%) ulcer cases (3 gastric, 2 peptic, and 2 duodenal ulcer), all reported in the oxaprozin potassium group. Of the seven cases: two had a history of GI ulcer; two had a history of gastroesophageal reflux; six were symptomatic (the reason for the detection of asymptomatic ulcer was not provided by the sponsor); one had ulcer complication expressed as slight bleeding; two had concomitant decreases in hemoglobin and hematocrit; two resulted in hospitalization; five were terminated early; and none was reported to have massive bleeding or perforation.

Melena (blood in stool) was reported in 4 cases (2 on oxaprozin potassium, 1 on oxaprozin, and 1 on placebo): three were considered GYN in origin. No ulcer or concomitant decreases in hemoglobin or hematocrit were reported in any of the melena cases.

(6) Abnormal laboratory findings

Laboratory abnormalities significantly outside the normal ranges were reported mainly as the changes in liver function tests and hematologic parameters as shown in Table 8. Twenty-two patients had increased SGOT and/or SGPT three times

above the upper limit of normal range: 9 of them (5 on oxaprozin salt, 2 on oxaprozin acid, and 2 on placebo) resolved spontaneously without interruption of the treatment; 11 (5 on oxaprozin salt and 2 on oxaprozin acid) recovered after the discontinuation of the test medication; and 2 were terminated early without follow up information available. Among the group of patients who had concurrent decreases in hemoglobin and hematocrit, one had gastric ulcer, one had peptic ulcer, and one had epistaxis in oxaprozin potassium group. Twelve patients had decreased white blood cell counts (WBC) below 3000/μL, but none was terminated early for the decreases in WBC.

(7) AE with respect to demographic characteristics

Adverse events reported in the demographic subgroups are summarized in Table 9. There were no statistically significant differences in the proportion of subjects who developed AEs when each pair of the sub-populations was compared: elderly versus non-elderly, male versus female, and Caucasian versus the other racial groups. In terms of the individual AEs, statistically significantly more elderly complained of constipation in the oxaprozin potassium group and complained of pain, flatulence, and tinnitus in the oxaprozin group; more non-elderly complained of influenza-like symptoms and sinusitis in the oxaprozin potassium group; more females reported coughing and sinusitis in the oxaprozin potassium group and accidental injury in the oxaprozin group.

5. Summary

The active drugs: oxaprozin potassium and oxaprozin, both performed statistically better than placebo in terms of the primary efficacy parameters: patient's global, physician's global, knee pain on weight bearing, and knee pain on motion. The positive results were supported by the findings of the WOMAC assessment. Oxaprozin potassium and oxaprozin were shown to be comparable in efficacy for the symptomatic relieve of OA based on the Q-statistics analysis.

Both active treatment groups had significantly more reports of AEs than the placebo group in the overall incidence, GI distress symptoms, and liver enzyme increases. There were more early terminations due to AEs in the active treatment groups than the placebo group, mostly because of the GI distress symptoms, and the finding was statistically significant when oxaprozin potassium was compared to placebo. There were 7 ulcer cases all reported in patients receiving oxaprozin potassium. Six of 7 were symptomatic and one had slight bleeding. Other than the GI ulcer cases, most of the 20 cases of AEs with serious outcomes were not considered as study drug related. The demographic characteristics such as age, gender, and race did not appear to have much a influence on AE reports.

6. Conclusion

This study provided substantial evidence that oxaprozin potassium 1200mg given once a day is effective for the symptomatic treatment of OA. Oxaprozin potassium appeared to expose patients to higher risks of upper GI adverse events than the oxaprozin acid formulation. The safety profile of oxaprozin potassium is otherwise similar to that of oxaprozin.

7. Recommendations

Oxaprozin potassium 1200mg once a day dosage is recommended for the symptoms and signs of osteoarthritis. The maximum daily dose of the potassium salt formulation should be limited to 1200mg because the ulcerogenic potential of the salt formulation at 1200mg is significantly greater than that of the acid formulation and the safety data on oxaprozin potassium 1800mg were very limited.

8. Tables

Table 1. Early termination from the study

Termination before the end of 24-week period						
Reason	***Lost to follow-up***	***Protocol violation***	***Non-compliance***	***Treatment failure***	***Adverse events***	***Total***
OxK-1200	5 (2%)	1 (0%)	16 (5%)	36 (11%)	81 (25%)	139 (43%)
Ox-1200	8 (3%)	1 (0%)	17 (5%)	49 (15%)	61 (19%)	136 (43%)
Placebo	5 (3%)	0 (0%)	6 (4%)	52 (32%)	20 (12%)	83 (52%)
Total	18	2	39	137	162	358

Table 2. Drug exposure

Number (%) of subjects exposed to the test drug						
Duration (wecks)	***24***	***≥18***	***≥12***	***≥6***	***≥2***	***<2***
OxK-1200	183 (57%)	193 (60%)	212 (66%)	232 (72%)	280 (87%)	42 (13%)
Ox-1200	184 (58%)	190 (59%)	214 (67%)	245 (77%)	289 (90%)	31 (10%)
Placebo	78 (48%)	80 (50%)	90 (56%)	102 (63%)	130 (81%)	31 (19%)

Table 3. QOL assessment: SF-36 Health Survey

SF-36 Health Survey	*Physical functioning*	*Role-physical*	*Bodily pain*	*General health*	*Vitality*	*Social functioning*	*Role-emotional*	*Mental health*
Statistically significant differences in changes from baseline at scheduled visits (weeks 2, 6, and 24)								
OxK-1200>Placebo	2, 6	2	2, 6					
Ox-1200>Placebo	2, 6, 24	2	2, 6, 24		6			
Ox-1200>OxK-1200	24							

Table 4. QOL assessment: WOMAC

WOMAC	*Pain*	*Stiffness*	*Physical function*
Statistically significant differences in changes from baseline at scheduled visits (weeks 2, 6, and 24)			
OxK-1200 > Placebo	2, 6, 24	2, 6, 24	2, 6, 24
Ox-1200 > Placebo	2, 6, 24	2, 6, 24	2, 6, 24

Table 5. QOL assessment: MOS Pain Survey

MOS Pain Survey	*Effects of pain*	*Pain severity*	*Pain interfered*
Statistically significant differences in changes from baseline at scheduled visits (weeks 2, 6, and 24)			
OxK-1200 > Placebo	2, 6	2, 6	2
Ox-1200 > Placebo	2, 6	2, 6, 24	2
Ox-1200>OxK-1200		24	

Table 6. Most frequently reported AE's and body systems affected

Body systems	*AE (COSTART terms)*	*OxK-1200*	*Ox-1200*	*Placebo*
		Number (%) subjects with AE		
Digestive	Dyspepsia	54 (17) *	41 (13) *	8 (5)
	Nausea	43 (13) *†	20 (6)	5 (3)
	Abdominal pain	35 (11) *	29 (9) *	4 (2)
	Diarrhea	27 (8)	21 (7)	9 (6)
	Constipation	24 (7) *	19 (6) *	1 (1)
	Flatulence	19 (6)	12 (4)	3 (2)
Metabolic and nutritional	SGOT increased	20 (6) *	11 (3) *	0
	SGPT increased	18 (6) *	13 (4)	2 (1)
Body as a whole	Headache	29 (9)	31 (10)	17 (11)
	Flu syndrome	21 (7)	10 (3)	6 (4)
Respiratory	Pharyngitis	38 (12)	43 (13)	14 (9)
	Cough increased	16 (5) †	4 (1)	3 (2)
Musculoskeletal	Arthralgia	15 (5)	15 (5)	10 (6)

Note: * means the active treatment groups had statistically greater AE rates than placebo group; † means the oxaprozin potassium group had also statistically greater AE rates than the oxaprozin group.

7. Serious adverse events

Patient #	*Adverse events*	*Length of treatment*	*Test drug related**	*Complications*
Oxaprozin Potassium Group				
7-0818	GE reflux, peptic ulcer with H. pylori infection	4 months	Could not be excluded	
8-0552	Pharyngitis	3 months	Less likely	
16-0741	Pneumonia, anemia, and hypotension	2 months	Less likely	
23-0395	Epistaxis	9 weeks	Less likely	
20-0117	Furuncle leading to cellulitis	1.5 weeks	Less likely	
12-0696	Shortness of breath and vaginal bleeding	6 weeks		Death
20-0332	Pneumonia	7 weeks	Not related	
18-0285	Syncope and cerebrovascular findings by MRI	3.5 weeks	Could not be excluded	
13-0495	Moniliasis (also gastroenteritis and duodenal ulcer with slight bleeding)	2 days	Could not be excluded	
20-0319	Gastric ulcer	3 months	Likely	
Oxaprozin Acid Group				
30-0773	Syncope and bradycardia, 2 episodes	4 and 5 months	Less likely	Controlled by pacemaker
30-0606	Prostate cancer	5 months	No	

13-0487	Cataract surgery	5 months	No	
5-0793	Pulmonary edema and respiratory insufficiency	11 weeks		Death
25-0511	Pneumonia and pyelonephritis	1 month	Less likely	
13-0498	Breast cancer	7 weeks	No	
19-0301	Angina	3 months	Could not be excluded	Corrected by coronary bypass surgery
Placebo Group				
13-0485	Acute myocardial infarction	4 months	Less likely	Death
1-0766	Chest pain	10 days	Less likely	Chronic obstructive pulmonary disease
30-0604	Hip fracture	6 weeks	Less likely	

*Note: the relationship between the event and the test drug was extracted based on the primary investigators' assessment.

Table 8. Remarkable laboratory abnormalities

	OxK-1200	*Ox-1200*	*Placebo*
Remarkable changes in lab tests	***Number (%) subjects***		
SGOT and/or SGPT ≥3x ULN	12 (3.7%)	8 (2.5%)	2 (1.2%)
SGPT ≥3x ULN only	6 (1.9%)	5 (1.6%)	2 (1.2%)
Alkaline phosphatase ≥1.25 ULN	0	8 (2.5%)	1 (0.6%)
Bilirubin ≥1.5 ULN	1 (0.3%)	0	1 (0.6%)
Hgb ↓ ≥2 g/dL and Hct ↓ ≥0.05	9 (2.8%)	7 (2.2%)	0
Hct ↓ ≥0.05 only	20 (6.2%)	23 (7.2%)	8 (5.0%)
White blood cells <3000/μL	7 (2.2%)	2 (0.6%)	3 (1.9%)
Platelet <100,000/μL	1 (0.3%)	1 (0.3%)	0
Blood urea nitrogen ≥2x ULN	1 (0.3%)	0	0

Table 9. AE with respect to demographic characteristics

	OxK-1200	*Ox-1200*	*Placebo*
Population	Number of subjects with AE (% wrt population exposed)		
Total	263/322 (82)	244/320 (76)	106/161 (66)
Elderly (≥65)	109/135 (81)	85/112 (76)	46/67 (69)
Age <65	154/187 (82)	159/208 (76)	60/94 (64)
Male	69/93 (74)	68/103 (66)	29/55 (53)
Female	194/229 (85)	176/217 (81)	77/106 (73)
Caucasian	221/271 (82)	203/266 (76)	82/129 (64)
Other	41/51 (80)	41/54 (76)	24/32 (75)

V. SAFETY REVIEW

THE FORMAT OF THE SAFETY REVIEW

1. Safety data from the 24-week multiple-dose study

2. Safety data from the short-term and single-dose studies

    (1) Study description
    (2) Drug exposure
    (3) Incidence of adverse events
    (4) Serious adverse events
    (5) Early terminations due to adverse events

3. Additional study completed after NDA submission

4. Safety of oxaprozin (Daypro)

    (1) Post-approval clinical studies of oxaprozin
    (2) Post-marketing surveillance on oxaprozin
    (3) Literature reports on safety of oxaprozin

5. Summary

6. Conclusion

7. Recommendations

8. Tables

1. Safety data from the 24-week multiple-dose study

The details are presented in the review of osteoarthritis in section IV. The information will be briefly summarized here.

A total of 803 patients, mostly elderly and Caucasians, received at least 1 dose of the study medication: 322 received oxaprozin potassium, 320 received oxaprozin, and 161 received placebo. About 50% patients had drug exposure for 24 weeks and two thirds had it for 12 weeks. There were no statistically significant differences among the treatment groups with regard to the baseline demographic and disease characteristics.

Subjects on oxaprozin potassium and oxaprozin had significantly more reports of adverse events (AEs) than on placebo in overall incidence, GI distress symptoms, and liver enzyme increases. There were more early terminations due to AEs in the active treatment groups than the placebo group, mostly because of the GI distress symptoms, and the finding was statistically significant when oxaprozin potassium was compared to placebo. There were 7 ulcer cases all reported in patients receiving oxaprozin potassium. Six of 7 were symptomatic and one had slight bleeding. Other than the GI ulcer cases, most of the 20 cases of AEs with serious outcomes were not considered as study drug related. The demographic characteristics such as age, gender, and race did not appear to have much an influence on AE reports.

2. Safety data from the short-term and single-dose studies

(1) Study description

In addition to the 6-month osteoarthritis study, there were 5 single-dose analgesic studies and 5 pharmacokinetic (PK) studies, of which four were single-dose studies and one was a multiple-dose study of 7 days in duration. The study designs are summarized in Table 1. The safety data obtained from these trials are of limited use because of the short exposure to the study drugs and the small sample size of the individual studies. Nevertheless, they are pooled together to provide some information on the type and frequency of the adverse events.

(2) Drug exposure

Drug exposures for single-dose studies and one-week PK study are presented in Table 1 at the end of the section. There was a total of 1490 subjects who received at least one single-dose of a test drug: 665 received oxaprozin potassium (of which 36 received 1800mg), 80 received oxaprozin potassium/oxaprozin bilayer tablet, 249 received oxaprozin, 223 received ibuprofen, and 273 received placebo.

(3) Incidence of adverse events

As shown in Table 2, adverse events (AEs) were reported in about 40 to 60% subjects: 38% of subjects on oxaprozin potassium, 39% on oxaprozin, 43% on ibuprofen, and 40% on placebo in dental studies; 56% on oxaprozin potassium and 50% (6 of 12) on oxaprozin in the single-dose PK studies; and 47% (7 of 15) on oxaprozin potassium and 46% (6 of 13) on oxaprozin in the one-week PK study. There were no statistically significant differences between the treatment groups in the overall rates of adverse events. In terms of individual AEs based on the pooled data in dental studies, there were significantly more reports of dyspepsia in patients on oxaprozin potassium than placebo (10 versus 2 cases, or 3.6% versus 0.7%). On the other hand, vomiting was reported by significantly more placebo patients than patients on oxaprozin potassium (20 versus 7 cases, or 7.3% versus 2.5%). For the short-term and single-dose studies in general, the most frequently (≥3 % of subjects) reported were GI symptoms such as abdominal pain, nausea, flatulence, dyspepsia, vomiting, diarrhea, and constipation. Other frequently

reported AEs were headache, injection site inflammation, fever, dizziness, rhinitis, pharyngitis, arthralgia, and pruritus.

(4) Serious adverse events

There were no reports of death or other AEs leading to serious outcomes in any dental or PK studies.

(5) Early terminations due to adverse events

In dental studies, 2 subjects receiving oxaprozin potassium 1200mg discontinued early due to adverse events for the reasons of severe nausea and vomiting within 15 minutes after dosing in 1 case and moderate oral hemorrhage 3 hours after dosing in the second case. In the one-week PK study, one subject on oxaprozin 1200mg discontinued early because of rash, which occurred on day 6 and was considered study drug related.

3. Additional study completed after the NDA submission

Study 014 was a multiple-dose, double-blind, randomized, parallel, placebo-controlled study of 6 weeks in duration in patients with OA. A total of 378 patients were treated: 124 with oxaprozin potassium 1200mg a day, 127 were treated with etodolac 400mg twice a day, and 127 were treated with placebo. There were no statistically significant differences among the treatment groups with regard to demographic characteristics such as age, gender, and race. The number and percentage of patients exposed to the test drugs for more than 2 weeks included: 104 (84%) in the oxaprozin potassium group, 119 (94%) in the etodolac group, and 108 (85%) in the placebo group.

Adverse events (AEs) were reported in 57% patients on oxaprozin potassium, 50% on etodolac, and 43% on placebo. The most frequently (≥5 % of subjects) reported were GI symptoms: nausea, dyspepsia, abdominal pain, constipation, and diarrhea; and other symptoms such as headache, anemia, upper respiratory tract infection, rhinitis, and flu symptoms. The oxaprozin potassium group had statistically significantly more AEs reported than the placebo group in the overall incidence, GI symptoms in general, nausea, dyspepsia, abdominal pain, constipation, increase in SGOT, and flu symptoms. There were also statistically significantly more incidence in general GI symptoms, nausea, increase in SGPT, and anemia in the oxaprozin potassium group than in the etodolac group.

A total of 31 patients discontinued early due to adverse events: 20 (16%) on oxaprozin potassium, 8 (6%) on etodolac, and 3 (2%) on placebo, significantly more on oxaprozin potassium than either etodolac or placebo, mainly due to GI symptoms.

No deaths were reported. There were 3 serious events. The first case had hemorrhagic gastric ulcer and gastritis accompanied by GI distress symptoms and melena (bloody stools) after 9 days of oxaprozin potassium treatment and was considered to be study drug related. The second case had questionable unstable angina 27 days after the initial dose of oxaprozin potassium and was thought less likely to be study drug related. The third case had non-hemorrhagic cerebrovascular accident and suspected myocardial infarction after 14 days being on etodolac. The drug-association of the event was uncertain based on the investigator's opinion.

There were no statistically significant differences between the treatment groups in terms of the clinically meaningful lab abnormalities.

Significant contribution of age, gender or race to the adverse event occupance was not shown.

4. Updated safety information for Daypro

(1) Post-approval clinical studies of Daypro

There have been 16 clinical trials since the market approval of Daypro. A total of 1280 patients were included in the studies and 699 received oxaprozin ranging from a single dose of either 600mg, 1200mg, or 1800mg, to daily doses of 1200mg for 6-8 weeks or 1800mg for 4 weeks as shown in Table 3 at the end of section. The details about the study design, duration, the treatment groups, as well as the number of subjects per treatment group are on page 11 in Appendix B.

Based on the pooled data, as summarized on pages 12 to 13 in Appendix B, the most frequently reported AEs were GI symptoms such as abdominal pain, dyspepsia, nausea, diarrhea, constipation, flatulence, and melena. Other frequently reported AEs were headache, dizziness, upper respiratory symptoms, abnormal hepatic function, etc. Subjects on multiple daily doses of 1800mg appeared to have more reports of upper GI distress symptoms, suggesting a dose-response relationship.

There was one case of gastric ulcer, which was detected following discontinuation of study medication; 13 cases of melena, 8 of which were positive hemoccult findings; 2 cases of elevated SGOT and SGPT and 8 cases of abnormal hepatic function.

(2) Post-marketing surveillance on Daypro

During the first 4 years (October 92 to October 96) following the market approval, oxaprozin was distributed to approximately —— people. The sponsor received reports of 2597 adverse events, of which 448 were categorized as serious (the events with outcomes of death, hospitalization, disabled, congenital abnormality, and life-threatening). The most frequently reported and remarkable events were upper GI distress symptoms such as dyspepsia (98 events), nausea (88), and abdominal pain (86); GI hemorrhage (58); allergic reactions (67); and skin reactions such as rash (104), pruritus (54), and urticaria (40). A summary table of individual events can be found on pages 14 to 21 in Appendix B.

Also presented in Appendix B on page 22 is an overview of the counts and percentage of fatal events over total adverse events, where an NSAID was suspected as a cause of the event, for all NSAIDs based on the data collected through the Spontaneous Reporting System (SRS) at FDA from 1969 to September 1997. Attempts to interpret data based on spontaneous reports could be misleading for many reasons. Not all adverse events were reported and there are a number of ways to have counts duplicated for a single event. The numbers reported are influenced by the pattern of usage (intermittent versus chronic), the year in which the drug was approved, length of time in the market, and familiarity with or novelty of an observed adverse reaction. The counts of events reflect reporting frequency but not the actual incidence of adverse reactions, because no information was provided on the number of patients exposed to the product for the purpose of risk ratio estimation. Though the events were included in the list only if a given NSAID was suspected, the reaction may be due to underlying disease, concomitant medication, or other causes since most reports were not accompanied by a detailed differential diagnosis. Nevertheless, the percentage of fatal events out of all events reported for oxaprozin was less than 2%, not an alarming figure.

(3) Literature reports on the safety of Daypro

The multiple-dose studies of oxaprozin for OA/RA that had larger sample size (at least 40 patients on oxaprozin) were selected for the review purposes. As shown on pages 23 to 24 in Appendix B, the most frequent AEs reported in the literature were GI symptoms, especially, the upper GI distress symptoms. The incidence of AEs in general was lower than the ones reported in the clinical trials conducted by the sponsor.

5. Summary

In the clinical trials designed to study oxaprozin potassium, a total of 2599 subjects received at least one dose of study medication to date, including 1039 received oxaprozin potassium, 80 received oxaprozin potassium/oxaprozin bilayer tablet, 569 received oxaprozin, 223 received ibuprofen, 127 received etodolac, and 561 received placebo. The exposure to oxaprozin potassium ranged from a single dose up to 1800mg to multiple doses of 1200mg for 24 weeks (in 183 patients in OA study).

The most frequent and remarkable adverse events associated with oxaprozin potassium were upper GI distress symptoms. There were 2 hemorrhagic ulcers and 6 symptomatic ulcers, all reported in the oxaprozin potassium group, suggesting an increased GI risk associated with the salt formulation of oxaprozin.

Based on the post-approval clinical studies, spontaneous AE reports, and literature reports, there were no dramatic changes in the safety profile of oxaprozin acid.

6. Conclusion

Oxaprozin potassium once daily dosing is considered reasonably safe. There is a potential for increased ulcer complications associated with the salt formulation in comparison to the acid formulation. One would expect to obtain safety data from at least 300 patients who were actually exposed to oxaprozin potassium for at least 6 months, instead of just 183 patients as reported in this NDA. However, the information had not been clearly communicated between the division and the sponsor. Therefore, the amount of safety information on oxaprozin potassium 1200mg in addition to the safety database of Daypro will be accepted to support the safety of 1200mg once daily dosing.

7. Recommendations

Oxaprozin potassium 1200mg once daily dosing is recommended for the symptomatic treatment of osteoarthritis. The sponsor should consider further safety studies to assess the scope of its GI toxicity. The maximum daily dose of the potassium salt formulation should be limited to 1200mg

8. Tables

Table 1. Study design and duration in single-dose & short-term studies

Studies	***Five single-dose dental studies***	***Four single-dose PK studies***	***One multiple-dose PK study***
Study #	016, 007, 009, 010, 004	001, 008, 012, 013	005
Study design	Randomized double-blind (single-blind in 004) placebo-controlled parallel	Randomized open parallel (3-way crossover in study 008)	Randomized open parallel
Drug (mg)	**Number of subjects exposed**		
	single dose		**daily dosing for 1 wk**
OxK-1800		36	
OxK-1200	280	146	15
OxK-900	51		
OxK-600	51	36	
OxK-300	50		
OxK/Ox-1200	56	12	12
Ox-1200	224	12	13
Ibu-400	223		
Placebo	273		

Table 2. Most frequently reported AEs in dental and PK studies

AE	*Single-dose dental studies (pooled)*				
	OxK	***OxK/Ox-1200***	***Ox-1200***	***Ibu-400***	***Placebo***
# subjects	432	56	224	223	273
# subj with any AE (%)	166 (38)	16 (29)	88 (39)	96 (43)	109 (40)
Inj site inflam	40 (10)	0	8 (4)	15 (7)	26 (10)
Headache	39 (9)	5 (9)	25 (11)	34 (15)	34 (13)
Dizziness	17 (4)	3 (5)	12 (5)	13 (6)	12 (4)
Nausea	39 (9)	9 (16)	27 (12)	23 (10)	38 (14)
Dyspepsia	12 (3)	0	3 (1)	5 (2)	2 (1)
Vomiting	12 (3)	2 (4)	8 (4)	8 (4)	20 (7)

AE	*Single-dose PK studies (pooled)*			*Multiple-dose PK study*		
	OxK	***OxK/Ox-1200***	***Ox-1200***	***OxK***	***OxK/Ox-1200***	***Ox-1200***
# subjects	218	12	12	15	12	13
# subj with any AE (%)	122 (56)	8 (67)	6 (50)	7 (47)	6 (50)	6 (46)
Fever	13 (6)	0	0			
Headache	33 (15)	1 (8)	3 (25)	2 (13)	0	0
Abdom pain	12 (6)	0	0	3 (20)	3 (25)	1 (8)
Flatulence	13 (6)	0	0			
Diarrhea	9 (4)	0	1 (8)			
Nausea	11 (5)	1 (8)	0			
Constipation	7 (3)	0	0	0	2 (17)	0
Arthralgia	8 (4)	0	0			
Rhinitis	13 (6)	1 (8)	1 (8)			
Pharyngitis	8 (4)	0	1 (8)			
Pruritus	6 (3)	0	0			

Table 3. Study duration versus dose level of Daypro in post-marketing studies

Oxaprozin dosing	*Number of subjects*	*Study number*
600mg single dose	74	020, 027
1200mg single dose	38	027
1200mg once daily, 4-28 days	197	004, 013, 016, 017 023, 025, 026, 029
1200mg once daily, 6-8 weeks	337	004, 009, 021, 022
1800mg single dose	62	015, 027
1800mg once daily, for 8 days	25	028
1800mg daily in 3 divided doses for 4 weeks	82	010

Table 4. Duration of oxaprozin potassium treatment in all clinical trials

Drug (mg)	*Number of subjects*				
	Single dose (9 studies)	*Multiple dose*			*Total*
		1 week	*6 weeks*	*24 weeks*	
OxK-1800	36 (single dose); 20 (divided doses in 1 day)				56
OxK-1200	426	15	124	322	887
OxK-900	51				51
OxK-600	87				87
OxK-300	50				50
OxK/Ox-1200	68	12			80
Ox-1200	236	13		320	569
Ibu-400	223				223
Eto-400 BID			127		127
Placebo	273		127	161	561

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_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

VII. APPENDIX A

APPENDIX A

1. Abbreviations and definitions

    (1) Common abbreviations
    (2) Efficacy parameters
    (3) Statistical significance and pairwise comparisons

2. Primary efficacy parameters in dental studies

3. Efficacy parameters in osteoarthritis study

(1) Primary efficacy parameters	Tables 21-25
(2) Secondary efficacy parameters	Tables 26-39

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Table 21. Knee pain on weight-bearing in study 006
Table 22. Knee pain on motion in study 006
Table 23. Patient's global in study 006
Table 24. Physician's global in study 006
Table 25. Q ratio and boundaries for primary efficacy parameters in study 006

Table 26. SF-36 Health Survey - physical functioning
Table 27. SF-36 Health Survey - role: physical
Table 28. SF-36 Health Survey - bodily pain
Table 29. SF-36 Health Survey - general health
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Table 31. SF-36 Health Survey - social functioning
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Table 34. WOMAC Osteoarthritis Index - pain
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Table 37. MOS Pain Survey - effects of pain
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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Table 21. Assessment of Knee Pain on Weight-Bearing: Study N48-95-02-006

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INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 53
ASSESSMENT OF KNEE PAIN ON WEIGHT-BEARING (PART 2 OF 2)
CHANGE FROM BASELINE (a,b,c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	-0.6	-0.9	-0.8
STD DEV	0.91	0.91	0.85
LS MEAN (d)	-0.6	-0.8	-0.8
WEEK 6			
MEAN CHANGE	-0.7	-0.9	-0.9
STD DEV	1.01	0.96	0.94
LS MEAN (d)	-0.6	-0.9	-0.9
WEEK 12			
MEAN CHANGE	-0.7	-0.9	-0.9
STD DEV	1.08	0.96	0.96
LS MEAN (d)	-0.7	-0.9	-0.9
WEEK 24 **			
MEAN CHANGE	-0.7	-0.8	-0.8
STD DEV	1.09	0.94	0.95
LS MEAN (d)	-0.7	-0.8	-0.8

P-VALUES FOR OVERALL COMPARISONS (d): WEEK 2: 0.001 *** WEEK 6: 0.001 *** WEEK 12: 0.004 ** WEEK 24: 0.081
P-VALUES FOR TREATMENT*CENTER INTERACTION (e): WEEK 2: 0.971 WEEK 6: 0.677 WEEK 12: 0.777 WEEK 24: 0.608

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.940	0.000 ***	0.000 ***
WEEK 6	0.460	0.000 ***	0.003 **
WEEK 12	0.829	0.002 **	0.003 **
WEEK 24	0.666	0.029 *	0.068

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very Severe.
(b) This table is based on the last observation carried forward approach.
(c) Change from baseline = visit score - baseline score. Negative values indicate improvement.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
** Week 24 or final visit

Table 22. Assessment of Knee Pain on Motion: Study N48-95-02-006

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INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE S4
ASSESSMENT OF KNEE PAIN ON MOTION (PART 2 OF 2)
CHANGE FROM BASELINE (a,b,c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	-0.7	-1.0	-1.0
STD DEV	0.98	0.93	0.92
LS MEAN (d)	-0.7	-1.0	-0.9
WEEK 6			
MEAN CHANGE	-0.8	-1.1	-1.1
STD DEV	1.03	1.02	1.01
LS MEAN (d)	-0.8	-1.1	-1.2
WEEK 12			
MEAN CHANGE	-0.9	-1.1	-1.1
STD DEV	1.11	0.99	1.02
LS MEAN (d)	-0.9	-1.1	-1.1
WEEK 24 ++			
MEAN CHANGE	-0.7	-1.1	-1.1
STD DEV	1.14	1.00	1.01
LS MEAN (d)	-0.8	-1.1	-1.1

P-VALUES FOR OVERALL COMPARISONS (d): WEEK 2: 0.001 *** WEEK 6: 0.000 *** WEEK 12: 0.021 * WEEK 24: 0.001 ***
P-VALUES FOR TREATMENT*CENTER INTERACTION (e): WEEK 2: 0.531 WEEK 6: 0.803 WEEK 12: 0.642 WEEK 24: 0.771

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.532	0.001 ***	0.000 ***
WEEK 6	0.338	0.000 ***	0.001 ***
WEEK 12	0.446	0.006 **	0.034 *
WEEK 24	0.715	0.001 ***	0.001 ***

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very Severe.
(b) This table is based on the last observation carried forward approach.
(c) Change from baseline = visit score - baseline score. Negative values indicate improvement.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
++ Week 24 or final visit

Table 23. Patient's Global Assessment of Osteoarthritis: Study N48-95-02-006

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INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 55
PATIENT'S GLOBAL ASSESSMENT OF OSTEOARTERITIS (PART 2 OF 2)
CHANGE FROM BASELINE (a,b,c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	-0.6	-0.9	-0.9
STD DEV	0.97	0.89	0.86
LS MEAN (d)	-0.5	-0.8	-0.9
WEEK 6			
MEAN CHANGE	-0.7	-0.9	-1.0
STD DEV	1.02	0.94	0.92
LS MEAN (d)	-0.6	-0.8	-1.0
WEEK 12			
MEAN CHANGE	-0.7	-0.9	-0.9
STD DEV	1.07	0.96	0.93
LS MEAN (d)	-0.7	-0.9	-0.9
WEEK 24 **			
MEAN CHANGE	-0.7	-0.9	-0.9
STD DEV	1.18	1.00	0.96
LS MEAN (d)	-0.7	-0.8	-0.9

P-VALUES FOR OVERALL COMPARISONS (d): WEEK 2: 0.000 *** WEEK 6: 0.000 *** WEEK 12: 0.008 ** WEEK 24: 0.068
P-VALUES FOR TREATMENT*CENTER INTERACTION (e): WEEK 2: 0.599 WEEK 6: 0.835 WEEK 12: 0.602 WEEK 24: 0.172

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.617	0.000 ***	0.000 ***
WEEK 6	0.050 *	0.000 ***	0.010 **
WEEK 12	0.819	0.004 **	0.007 **
WEEK 24	0.574	0.023 *	0.069

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) 0 = Very Good, 1 = Good, 2 = Fair, 3 = Poor, 4 = Very Poor.
(b) This table is based on the last observation carried forward approach.
(c) Change from baseline = visit score - baseline score. Negative values indicate improvement.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
** Week 24 or final visit

Table 24. Physician's Global Assessment of Osteoarthritis: Study N48-95-02-006

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 56
PHYSICIAN'S GLOBAL ASSESSMENT OF OSTEOARTHRITIS (PART 2 OF 2)
CHANGE FROM BASELINE (a,b,c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	-0.5	-0.9	-0.9
STD DEV	0.89	0.87	0.81
LS MEAN (d)	-0.5	-0.9	-0.9
WEEK 6			
MEAN CHANGE	-0.6	-0.9	-1.0
STD DEV	0.93	0.92	0.87
LS MEAN (d)	-0.6	-0.9	-1.0
WEEK 12			
MEAN CHANGE	-0.7	-0.9	-1.0
STD DEV	1.00	0.95	0.87
LS MEAN (d)	-0.7	-0.9	-0.9
WEEK 24 ++			
MEAN CHANGE	-0.7	-0.9	-0.9
STD DEV	1.10	0.95	0.89
LS MEAN (d)	-0.6	-0.9	-0.9

P-VALUES FOR OVERALL COMPARISONS (d): WEEK 2: 0.000 *** WEEK 6: 0.000 *** WEEK 12: 0.001 *** WEEK 24: 0.004 **
P-VALUES FOR TREATMENT*CENTER INTERACTION (e): WEEK 2: 0.020 * WEEK 6: 0.614 WEEK 12: 0.186 WEEK 24: 0.111

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.414	0.000 ***	0.000 ***
WEEK 6	0.226	0.000 ***	0.000 ***
WEEK 12	0.490	0.000 ***	0.003 **
WEEK 24	0.644	0.001 ***	0.005 **

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) 0 = Very Good, 1 = Good, 2 = Fair, 3 = Poor, 4 = Very Poor.
(b) This table is based on the last observation carried forward approach.
(c) Change from baseline = visit score - baseline score. Negative values indicate improvement.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
++ Week 24 or final visit

Table 25. Q Ratio and Upper and Lower Bounds of Q for Primary Efficacy Variables: Study N48-95-02-006

1 *** FINAL *** DISK$SEAR5404:[SEAR5404.ISE.CLINPROG]TAB57.SAS 31MAR97 13:07

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 57
Q RATIO AND UPPER AND LOWER BOUNDS OF Q FOR PRIMARY EFFICACY VARIABLES (a,b)
ALL RANDOMIZED PATIENTS

	WEEK 2	WEEK 6	WEEK 12	WEEK 24 **
KNEE PAIN ON WEIGHT-BEARING				
OXP SALT (c)	-0.829	-0.935	-0.935	-0.826
OXP ACID (d)	-0.859	-0.906	-0.941	-0.816
QU(e)	1.088	1.165	1.120	1.163
Q	0.965	1.031	0.994	1.013
QL(e)	0.855	0.914	0.882	0.882
KNEE PAIN ON MOTION				
OXP SALT (c)	-0.953	-1.146	-1.134	-1.062
OXP ACID (d)	-1.019	-1.103	-1.103	-1.109
QU(e)	1.037	1.146	1.134	1.062
Q	0.936	1.039	1.028	0.957
QL(e)	0.844	0.942	0.932	0.863
PHYSICIAN'S GLOBAL ASSESSMENT OF OSTEOARTERITIS				
OXP SALT (c)	-0.935	-0.984	-0.979	-0.930
OXP ACID (d)	-0.888	-0.916	-0.934	-0.878
QU(e)	1.156	1.193	1.163	1.168
Q	1.043	1.075	1.047	1.036
QL(e)	0.943	0.970	0.943	0.920
PATIENT'S GLOBAL ASSESSMENT OF OSTEOARTERITIS				
OXP SALT (c)	-0.885	-0.978	-0.929	-0.879
OXP ACID (d)	-0.875	-0.872	-0.928	-0.856
QU(e)	1.132	1.262	1.125	1.175
Q	1.012	1.122	1.000	1.026
QL(e)	0.904	0.999	0.890	0.897

(a) Q = (mean change from the baseline for oxaprozin potassium) / (mean change from the baseline for oxaprozin acid).
(b) This table is based on the last observation carried forward approach.
(c) Oxp Salt = mean change from the baseline for oxaprozin potassium.
(d) Oxp Acid = mean change from the baseline for oxaprozin acid.
(e) QU and QL are the upper and lower bounds of the 95% confidence interval for the ratio Q (based on Fieller's theorem).
** Week 24 or final visit

Table 26. SF-36 Health Survey - Physical Functioning: Study N48-95-02-006

1 *** FINAL *** DISK$SEAR5404:[SEAR5404.ISE.CLINPROG]TAB58.SAS 31MAR97 13:09

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 58.1
SF-36 HEALTH SURVEY - PHYSICAL FUNCTIONING (PART 2 OF 2)
CHANGE FROM BASELINE (a, b, c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	-0.3	6.1	4.3
STD DEV	17.29	18.54	17.25
LS MEAN (d)	-1.1	5.2	3.7
WEEK 6			
MEAN CHANGE	0.8	6.5	6.5
STD DEV	21.77	20.53	18.56
LS MEAN (d)	0.1	6.1	6.4
WEEK 24 **			
MEAN CHANGE	2.8	8.0	4.6
STD DEV	23.61	20.82	19.79
LS MEAN (d)	2.0	7.7	4.6
P-VALUES FOR OVERALL COMPARISONS (d):	WEEK 2: 0.000 ***	WEEK 6: 0.001 ***	WEEK 24: 0.007 **
P-VALUES FOR TREATMENT*CENTER INTERACTION (e):	WEEK 2: 0.931	WEEK 6: 0.266	WEEK 24: 0.163

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.253	0.003 **	0.000 ***
WEEK 6	0.856	0.000 ***	0.001 ***
WEEK 24	0.041 *	0.173	0.003 **

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) Baseline, week 6 and week 24 are based on four week recall. Week 2 is based on one week recall.
(b) This table is based on the last observation carried forward approach.
(c) Score range from 0 to 100.
Change from baseline = visit score - baseline score. Positive values indicate improvement.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
** Week 24 or final visit.

Table 27. SF-36 Health Survey - Role - Physical: Study N48-95-02-006

1 *** FINAL *** DISK$SEAR5404:[SEAR5404.ISE.CLINPROG]TAB58.SAS 31MAR97 13:09

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 58.2
SF-36 HEALTH SURVEY - ROLE-PHYSICAL (PART 2 OF 2)
CHANGE FROM BASELINE (a, b, c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	0.3	14.8	11.0
STD DEV	38.83	39.36	36.33
LS MEAN (d)	0.3	14.3	10.1
WEEK 6			
MEAN CHANGE	2.5	11.0	9.8
STD DEV	44.21	40.71	39.36
LS MEAN (d)	2.6	11.1	8.9
WEEK 24 ++			
MEAN CHANGE	3.7	7.5	6.8
STD DEV	44.12	38.71	40.25
LS MEAN (d)	3.6	7.5	6.1
P-VALUES FOR OVERALL COMPARISONS (d):	WEEK 2: 0.000 ***	WEEK 6: 0.053	WEEK 24: 0.530
P-VALUES FOR TREATMENT*CENTER INTERACTION (e):	WEEK 2: 0.703	WEEK 6: 0.086	WEEK 24: 0.359
P-VALUES FOR TREATMENT COMPARISONS (f):			
	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.120	0.003 **	0.000 ***
WEEK 6	0.438	0.075	0.016 *
WEEK 24	0.628	0.465	0.260

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) Baseline, week 6 and week 24 are based on four week recall. Week 2 is based on one week recall.
(b) This table is based on the last observation carried forward approach.
(c) Score range from 0 to 100.
Change from baseline = visit score - baseline score. Positive values indicate improvement.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
++ Week 24 or final visit.

Table 28. SF-36 Health Survey - Bodily Pain: Study N48-95-02-006

1 *** FINAL *** DISK$SEAR5404:[SEAR5404.ISE.CLINPROG]TAB58.SAS 31MAR97 13:09

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 58.3
SF-36 HEALTH SURVEY - BODILY PAIN (PART 2 OF 2)
CHANGE FROM BASELINE (a, b, c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	3.1	12.0	10.1
STD DEV	18.30	18.30	17.71
LS MEAN (d)	1.9	11.8	10.0
WEEK 6			
MEAN CHANGE	4.9	11.0	10.7
STD DEV	19.46	19.96	20.44
LS MEAN (d)	3.8	11.2	10.7
WEEK 24 **			
MEAN CHANGE	5.3	9.7	7.4
STD DEV	22.15	21.42	20.91
LS MEAN (d)	4.1	10.0	7.6
P-VALUES FOR OVERALL COMPARISONS (d):	WEEK 2: 0.000 ***	WEEK 6: 0.000 ***	WEEK 24: 0.009 **
P-VALUES FOR TREATMENT*CENTER INTERACTION (e):	WEEK 2: 0.969	WEEK 6: 0.977	WEEK 24: 0.823
P-VALUES FOR TREATMENT COMPARISONS (f):			
	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.180	0.000 ***	0.000 ***
WEEK 6	0.757	0.000 ***	0.000 ***
WEEK 24	0.125	0.068	0.002 **

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) Baseline, week 6 and week 24 are based on four week recall. Week 2 is based on one week recall.
(b) This table is based on the last observation carried forward approach.
(c) Score range from 0 to 100.
Change from baseline = visit score - baseline score. Positive values indicate improvement.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
** Week 24 or final visit.

Table 29. SF-36 Health Survey - General Health: Study N48-95-02-006

1 *** FINAL *** DISK$SEAR5404:[SEAR5404.ISE.CLINPROG]TAB58.SAS 31MAR97 13:09

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 58.4
SF-36 HEALTH SURVEY - GENERAL HEALTH (PART 2 OF 2)
CHANGE FROM BASELINE (a, b, c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	-0.5	1.1	0.5
STD DEV	12.36	11.76	11.84
LS MEAN (d)	-0.9	0.7	0.2
WEEK 6			
MEAN CHANGE	-1.1	0.7	-0.0
STD DEV	12.61	13.06	13.11
LS MEAN (d)	-1.3	0.7	-0.0
WEEK 24 ++			
MEAN CHANGE	-0.3	0.4	-0.7
STD DEV	12.74	12.97	14.25
LS MEAN (d)	-0.4	0.5	-0.5
P-VALUES FOR OVERALL COMPARISONS (d):	WEEK 2: 0.342	WEEK 6: 0.252	WEEK 24: 0.568
P-VALUES FOR TREATMENT*CENTER INTERACTION (e):	WEEK 2: 0.160	WEEK 6: 0.923	WEEK 24: 0.946

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.552	0.327	0.143
WEEK 6	0.473	0.282	0.097
WEEK 24	0.312	0.912	0.473

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) Baseline, week 6 and week 24 are based on four week recall. Week 2 is based on one week recall.
(b) This table is based on the last observation carried forward approach.
(c) Score range from 0 to 100.
Change from baseline = visit score - baseline score. Positive values indicate improvement.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
++ Week 24 or final visit.

Table 30. SF-36 Health Survey - Vitality: Study N48-95-02-006

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 58.5
SF-36 HEALTH SURVEY - VITALITY (PART 2 OF 2)
CHANGE FROM BASELINE (a, b, c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	1.0	2.8	1.7
STD DEV	16.34	15.28	16.15
LS MEAN (d)	0.4	3.1	1.8
WEEK 6			
MEAN CHANGE	0.6	3.7	2.5
STD DEV	16.82	17.38	18.22
LS MEAN (d)	-0.4	3.9	2.3
WEEK 24 ++			
MEAN CHANGE	1.8	3.3	1.7
STD DEV	16.87	17.41	18.49
LS MEAN (d)	1.0	3.7	1.7
P-VALUES FOR OVERALL COMPARISONS (d):	WEEK 2: 0.145	WEEK 6: 0.029 *	WEEK 24: 0.177
P-VALUES FOR TREATMENT*CENTER INTERACTION (e):	WEEK 2: 0.375	WEEK 6: 0.691	WEEK 24: 0.245

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.241	0.332	0.055
WEEK 6	0.224	0.095	0.008 **
WEEK 24	0.141	0.657	0.100

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) Baseline, week 6 and week 24 are based on four week recall. Week 2 is based on one week recall.
(b) This table is based on the last observation carried forward approach.
(c) Score range from 0 to 100.
Change from baseline = visit score - baseline score. Positive values indicate improvement.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
++ Week 24 or final visit.

Table 31. SF-36 Health Survey - Social Functioning: Study N48-95-02-006

1 *** FINAL *** DISK$SEAR5404:[SEAR5404.ISE.CLINPROG]TAB58.SAS 31MAR97 13:09

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 58.6
SF-36 HEALTH SURVEY - SOCIAL FUNCTIONING (PART 2 OF 2)
CHANGE FROM BASELINE (a, b, c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	0.5	3.0	2.6
STD DEV	19.91	22.44	20.92
LS MEAN (d)	-0.6	3.5	3.0
WEEK 6			
MEAN CHANGE	1.7	0.7	0.3
STD DEV	22.77	23.79	24.65
LS MEAN (d)	0.0	1.0	0.3
WEEK 24 ++			
MEAN CHANGE	0.5	-0.4	-0.3
STD DEV	28.62	24.03	24.03
LS MEAN (d)	-1.0	0.4	-0.0
P-VALUES FOR OVERALL COMPARISONS (d):	WEEK 2: 0.082	WEEK 6: 0.874	WEEK 24: 0.823
P-VALUES FOR TREATMENT*CENTER INTERACTION (e):	WEEK 2: 0.939	WEEK 6: 0.044 *	WEEK 24: 0.053

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.708	0.062	0.031 *
WEEK 6	0.692	0.883	0.639
WEEK 24	0.831	0.653	0.534

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) Baseline, week 6 and week 24 are based on four week recall. Week 2 is based on one week recall.
(b) This table is based on the last observation carried forward approach.
(c) Score range from 0 to 100.
Change from baseline = visit score - baseline score. Positive values indicate improvement.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
++ Week 24 or final visit.

Table 32. SF-36 Health Survey - Role - Emotional: Study N48-95-02-006

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 58.7
SF-36 HEALTH SURVEY - ROLE-EMOTIONAL (PART 2 OF 2)
CHANGE FROM BASELINE (a, b, c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	0.2	4.9	8.1
STD DEV	37.10	42.01	40.51
LS MEAN (d)	0.2	6.3	6.0
WEEK 6			
MEAN CHANGE	1.5	2.7	6.8
STD DEV	40.32	43.08	41.51
LS MEAN (d)	1.6	4.3	4.9
WEEK 24 ++			
MEAN CHANGE	-2.4	4.3	5.3
STD DEV	42.41	45.67	42.64
LS MEAN (d)	-1.9	6.3	4.1
P-VALUES FOR OVERALL COMPARISONS (d):	WEEK 2: 0.144	WEEK 6: 0.623	WEEK 24: 0.072
P-VALUES FOR TREATMENT*CENTER INTERACTION (e):	WEEK 2: 0.921	WEEK 6: 0.992	WEEK 24: 0.922

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	*OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.932	0.078	0.067
WEEK 6	0.830	0.341	0.438
WEEK 24	0.447	0.096	0.022 *

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) Baseline, week 6 and week 24 are based on four week recall. Week 2 is based on one week recall.
(b) This table is based on the last observation carried forward approach.
(c) Score range from 0 to 100.
Change from baseline = visit score - baseline score. Positive values indicate improvement.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
++ Week 24 or final visit.

Table 33. SF-36 Healthy Survey - Mental Health: Study N48-95-02-006

(*** FINAL *** DISK5$EAR5404:[SEAR5404.ISE.CLINPROG]TAB58.SAS 31MAR97 13:09

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 58.8
SF-36 HEALTH SURVEY - MENTAL HEALTH (PART 2 OF 2)
CHANGE FROM BASELINE (a, b, c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	1.6	0.3	0.8
STD DEV	13.17	13.33	12.52
LS MEAN (d)	1.4	0.2	0.6
WEEK 6			
MEAN CHANGE	0.8	-0.0	-0.1
STD DEV	13.30	14.91	13.57
LS MEAN (d)	0.6	0.1	0.0
WEEK 24 ++			
MEAN CHANGE	0.1	0.4	-0.4
STD DEV	14.93	13.82	14.39
LS MEAN (d)	-0.0	0.5	-0.3
P-VALUES FOR OVERALL COMPARISONS (d):	WEEK 2: 0.619	WEEK 6: 0.889	WEEK 24: 0.733
P-VALUES FOR TREATMENT*CENTER INTERACTION (e):	WEEK 2: 0.119	WEEK 6: 0.537	WEEK 24: 0.710

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.693	0.510	0.328
WEEK 6	0.936	0.638	0.687
WEEK 24	0.435	0.824	0.677

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) Baseline, week 6 and week 24 are based on four week recall. Week 2 is based on one week recall.
(b) This table is based on the last observation carried forward approach.
(c) Score range from 0 to 100.
Change from baseline = visit score - baseline score. Positive values indicate improvement.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
++ Week 24 or final visit.

Table 34. WOMAC Osteoarthritis Index - Pain: Study N48-95-02-006

1 *** FINAL *** DISK$SEAR5404:[SEAR5404.ISE.CLINPROG]TAB59_1.SAS 02APR97 11:09

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 59.1
WOMAC OSTEOARTHRITIS INDEX - PAIN (PART 2 OF 2)
CHANGE FROM BASELINE (a,b,c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	-0.8	-2.3	-2.0
STD DEV	2.97	3.56	3.03
LS MEAN (d)	-0.7	-2.2	-2.0
WEEK 6			
MEAN CHANGE	-1.5	-2.5	-2.6
STD DEV	3.91	3.56	3.40
LS MEAN (d)	-1.4	-2.5	-2.6
WEEK 24 **			
MEAN CHANGE	-1.5	-2.4	-2.1
STD DEV	4.22	3.90	3.50
LS MEAN (d)	-1.3	-2.3	-2.1

P-VALUES FOR OVERALL COMPARISONS (d): WEEK 2: 0.000 *** WEEK 6: 0.000 *** WEEK 24: 0.012 *
P-VALUES FOR TREATMENT*CENTER INTERACTION (e): WEEK 2: 0.977 WEEK 6: 0.821 WEEK 24: 0.271

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.540	0.000 ***	0.000 ***
WEEK 6	0.507	0.000 ***	0.001 ***
WEEK 24	0.420	0.023 *	0.003 **

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) This table is based on the last observation carried forward approach.
(b) Score range from 0 (none) to 20 (extreme).
Change from baseline = visit score - baseline score. Negative values indicate improvement.
(c) All assessments are based on 2 week recall.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
** Week 24 or final visit.

Table 35. WOMAC Osteoarthritis Index - Stiffness: Study N48-95-02-006

(*** FINAL *** DISK$SEAR5404:[SEAR5404.ISE.CLINPROG]TAB59_2.SAS 02APR97 11:10

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 59.2
WOMAC OSTEOARTHRITIS INDEX - STIFFNESS (PART 2 OF 2)
CHANGE FROM BASELINE (a,b,c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	-0.3	-1.0	-1.0
STD DEV	1.48	1.66	1.45
LS MEAN (d)	-0.3	-1.0	-1.0
WEEK 6			
MEAN CHANGE	-0.6	-1.2	-1.2
STD DEV	1.82	1.62	1.44
LS MEAN (d)	-0.6	-1.2	-1.3
WEEK 24 **			
MEAN CHANGE	-0.6	-1.1	-1.1
STD DEV	1.95	1.71	1.54
LS MEAN (d)	-0.5	-1.1	-1.1

P-VALUES FOR OVERALL COMPARISONS (d): WEEK 2: 0.000 *** WEEK 6: 0.000 *** WEEK 24: 0.000 ***
P-VALUES FOR TREATMENT*CENTER INTERACTION (e): WEEK 2: 0.671 WEEK 6: 0.090 WEEK 24: 0.239

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT vs. OXP ACID	OXP SALT vs. PLACEBO	OXP ACID vs. PLACEBO
WEEK 2	0.813	0.000 ***	0.000 ***
WEEK 6	0.397	0.000 ***	0.000 ***
WEEK 24	0.777	0.000 ***	0.000 ***

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) This table is based on the last observation carried forward approach.
(b) Score range from 0 (none) to 8 (extreme).
Change from baseline = visit score - baseline score. Negative values indicate improvement.
(c) All assessments are based on 2 week recall.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
** Week 24 or final visit.

Table 36. WOMAC Osteoarthritis Index - Physical Function: Study N48-95-02-006

(*** FINAL *** DISK$SEAR5404:[SEAR5404.ISE.CLINPROG]TAB59_3.SAS 02APR97 11:11

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 59.3
WOMAC OSTEOARTHRITIS INDEX - PHYSICAL FUNCTION (PART 2 OF 2)
CHANGE FROM BASELINE (a,b,c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	-3.3	-7.6	-6.6
STD DEV	8.88	11.09	9.68
LS MEAN (d)	-3.0	-7.2	-6.8
WEEK 6			
MEAN CHANGE	-4.9	-8.8	-8.2
STD DEV	11.28	11.69	10.36
LS MEAN (d)	-4.6	-8.5	-8.5
WEEK 24 ++			
MEAN CHANGE	-5.2	-8.7	-8.7
STD DEV	12.30	12.38	11.08
LS MEAN (d)	-4.8	-8.4	-8.0

P-VALUES FOR OVERALL COMPARISONS (d): WEEK 2: 0.000 *** WEEK 6: 0.000 *** WEEK 24: 0.005 **
P-VALUES FOR TREAT*CENTER INTERACTION (e): WEEK 2: 0.529 WEEK 6: 0.236 WEEK 24: 0.164

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.595	0.000 ***	0.000 ***
WEEK 6	0.995	0.000 ***	0.000 ***
WEEK 24	0.130	0.041 *	0.001 ***

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) This table is based on the last observation carried forward approach.
(b) Score range from 0 (none) to 68 (extreme).
Change from baseline = visit score - baseline score. Negative values indicate improvement.
(c) All assessments are based on 2 week recall.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
++ Week 24 or final visit.

Table 37. MOS Pain Survey - Effects of Pain: Study N48-95-02-006

1 *** FINAL *** DISK$SEAR5404:[SEAR5404.ISE.CLINPROG]TAB60_1.SAS 14APR97 10:18

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 60.1
MOS PAIN SURVEY - EFFECTS OF PAIN (PART 2 OF 2)
CHANGE FROM BASELINE (a,b,c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	-6.7	-12.4	-11.5
STD DEV	18.30	18.70	18.06
LS MEAN (d)	-5.6	-11.7	-11.0
WEEK 6			
MEAN CHANGE	-7.1	-12.1	-11.8
STD DEV	21.03	21.58	20.86
LS MEAN (d)	-6.2	-12.2	-11.9
WEEK 24 ++			
MEAN CHANGE	-8.3	-9.9	-8.7
STD DEV	21.44	22.11	22.23
LS MEAN (d)	-7.1	-10.1	-8.8

P-VALUES FOR OVERALL COMPARISONS (d): WEEK 2: 0.001 *** WEEK 6: 0.005 ** WEEK 24: 0.348
P-VALUES FOR TREATMENT*CENTER INTERACTION (e): WEEK 2: 0.680 WEEK 6: 0.736 WEEK 24: 0.561

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.643	0.001 ***	0.000 ***
WEEK 6	0.826	0.004 **	0.002 **
WEEK 24	0.459	0.398	0.149

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) This table is based on the last observation carried forward approach.
(b) Scored from 0 to 100.
Change from baseline = visit score - baseline score. Negative values indicate improvement.
(c) Baseline, week 6 and week 24 are based on four week recall. Week 2 is based on one week recall.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
++ Week 24 or final visit.

Table 38. MOS Pain Survey - Pain Severity: Study N48-95-02-006

1 *** FINAL *** DISK$SEAR5404:[SEAR5404.ISE.CLINPROG]TAB60_2.SAS 14APR97 10:21

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 60.2
MOS PAIN SURVEY - PAIN SEVERITY (PART 2 OF 2)
CHANGE FROM BASELINE (a,b,c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	-0.3	-0.6	-0.5
STD DEV	0.69	0.75	0.68
LS MEAN (d)	-0.2	-0.6	-0.5
WEEK 6			
MEAN CHANGE	-0.3	-0.6	-0.5
STD DEV	0.80	0.83	0.75
LS MEAN (d)	-0.3	-0.6	-0.5
WEEK 24 ++			
MEAN CHANGE	-0.4	-0.5	-0.4
STD DEV	0.89	0.86	0.81
LS MEAN (d)	-0.3	-0.5	-0.4

P-VALUES FOR OVERALL COMPARISONS (d): WEEK 2: 0.000 *** WEEK 6: 0.000 *** WEEK 24: 0.013 *
P-VALUES FOR TREATMENT*CENTER INTERACTION (e): WEEK 2: 0.903 WEEK 6: 0.988 WEEK 24: 0.907

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.379	0.000 ***	0.000 ***
WEEK 6	0.578	0.000 ***	0.000 ***
WEEK 24	0.050 *	0.225	0.005 **

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) This table is based on the last observation carried forward approach.
(b) Change from baseline = visit score - baseline score. Negative values indicate improvement.
(c) Baseline, week 6 and week 24 are based on four week recall. Week 2 is based on one week recall.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
++ Week 24 or final visit.

Table 39. MOS Pain Survey - Pain Interfered: Study N48-95-02-006

1 *** FINAL *** DISK5$EAR5404:[$EAR5404.ISE.CLINPROG]TAB60_3.SAS 14APR97 10:25

INTEGRATED SUMMARY OF EFFECTIVENESS DATA
PROTOCOL N48-95-02-006

TABLE 60.3
MOS PAIN SURVEY - PAIN INTERFERED (PART 2 OF 2)
CHANGE FROM BASELINE (a,b,c)
ALL RANDOMIZED PATIENTS

	PLACEBO (N=161)	OXP ACID 1200 mg (N=320)	OXP SALT 1200 mg (N=322)
WEEK 2			
MEAN CHANGE	-6.5	-8.9	-8.9
STD DEV	11.03	10.80	11.50
LS MEAN (d)	-6.7	-8.7	-8.5
WEEK 6			
MEAN CHANGE	-3.1	-5.2	-4.9
STD DEV	10.54	10.73	11.17
LS MEAN (d)	-3.0	-4.8	-4.5
WEEK 24 ++			
MEAN CHANGE	-3.3	-4.6	-3.7
STD DEV	10.85	11.17	11.44
LS MEAN (d)	-3.2	-4.3	-3.3

P-VALUES FOR OVERALL COMPARISONS (d): WEEK 2: 0.030 * WEEK 6: 0.114 WEEK 24: 0.296
P-VALUES FOR TREATMENT*CENTER INTERACTION (e): WEEK 2: 0.979 WEEK 6: 0.145 WEEK 24: 0.314

P-VALUES FOR TREATMENT COMPARISONS (f):

	OXP SALT VS. OXP ACID	OXP SALT VS. PLACEBO	OXP ACID VS. PLACEBO
WEEK 2	0.789	0.022 *	0.012 *
WEEK 6	0.639	0.096	0.041 *
WEEK 24	0.182	0.844	0.199

***, **, * Statistically significant at p=0.001, 0.01, and 0.05 levels, respectively.
(a) This table is based on the last observation carried forward approach.
(b) Change from baseline = visit score - baseline score. Negative values indicate improvement.
(c) Baseline, week 6 and week 24 are based on four week recall. Week 2 is based on one week recall.
(d) Analysis of covariance model with treatment and center as factors and baseline value as covariate.
(e) Analysis of covariance model with treatment, center, treatment*center as factors and baseline value as covariate.
(f) Contrast statement from analysis of covariance model in (d).
++ Week 24 or final visit.

VIII. APPENDIX B

APPENDIX B

1. Tables

Table 1. Adverse events reported in the 24-week OA study
Table 2. Inventory of the post-marketing clinical studies of Daypro
Table 3. AEs reported in the post-marketing clinical studies of Daypro
Table 4. AEs for Daypro spontaneously reported to the sponsor
Table 5. Relative reporting frequency of fatal AEs for NSAIDs
Table 6. Safety data on Daypro from literature reports

2. References

3. Medical review of the labeling revisions for Daypro

1. Tables

Table 1. Adverse events reported in the 24-week OA study

(Note: Sev stands for severe AEs; Rel stands for probably study drug-related AEs)

	OxK-1200			*Ox-1200*			*Placebo*		
Subjects exposed	***N=322***			***N=320***			***N=161***		
Adverse events (by COSTART term)	***# subjects with AE***			***# subjects with AE***			***# subjects with AE***		
	N (%)	*Sev*	*Rel*	*N (%)*	*Sev*	*Rel*	*N (%)*	*Sev*	*Rel*
Total	*263 (82)*	*58*	*104*	*244 (76)*	*44*	*83*	*106 (66)*	*18*	*16*
⟨Total AE counts⟩	⟨751⟩	⟨72⟩	⟨160⟩	⟨646⟩	⟨59⟩	⟨114⟩	⟨235⟩	⟨22⟩	⟨22⟩
Body as a whole	⟨117⟩	⟨13⟩	⟨3⟩	⟨95⟩	⟨16⟩	⟨5⟩	⟨57⟩	⟨7⟩	⟨2⟩
Allergic reaction	4 (1)	0	0	5 (2)	2	0	2 (1)	1	0
Asthenia	13 (4)	0	2	8 (3)	0	2	4 (2)	0	0
Carcinoma	0	0	0	1 (0)	0	0	0	0	0
Cellulitis	1 (0)	1	0	1 (0)	0	0	0	0	0
Chills	2 (1)	0	0	1 (0)	0	0	1 (1)	0	0
Edema face	1 (0)	0	0	1 (0)	0	0	0 (0)	0	0
Fever	9 (3)	0	1	3 (1)	0	0	4 (2)	0	1
Flu syndrome	21 (7)	5	0	10 (3)	3	0	6 (4)	0	0
Headache	29 (9)	1	0	31 (10)	2	3	17 (11)	1	0
Heat stroke	0	0	0	1 (0)	0	0	0	0	0
Infection	1 (0)	0	0	1 (0)	0	0	0	0	0
Infection fungal	1 (1)	0	0	0	0	0	0	0	0
Injury accidental	3 (1)	0	0	9 (3)	2	0	3 (2)	1	0
Lab test abnormal	2 (1)	0	0	1 (0)	0	0	0 (0)	0	0
Malaise	0 (0)	0	0	1(0)	0	0	0 (0	0	0
Moniliasis	1 (0)	1	0	0	0	0	0	0	0
Pain	7 (2)	1	0	4 (1)	3	0	6 (4)	1	1
Pain back	12 (4)	3	0	8 (3)	1	0	5 (3)	1	0
Pain chest	7 (2)	1	0	1 (0)	0	0	5 (3)	1	0
Surgical procedure	3 (1)	0	0	8 (3)	3	0	4 (2	1	0

	OxK-1200			*Ox-1200*			*Placebo*		
Subjects exposed	***N=322***			***N=320***			***N=161***		
Adverse events (by COSTART term)	***# subjects with AE***			***# subjects with AE***			***# subjects with AE***		
	N (%)	***Sev***	***Rel***	***N (%)***	***Sev***	***Rel***	***N (%)***	***Sev***	***Rel***
Cardiovascular system	⟨20⟩	⟨8⟩	⟨3⟩	⟨15⟩	⟨5⟩	⟨0⟩	⟨9⟩	⟨1⟩	⟨0⟩
Angina pectoris	1 (0)	0	0	2 (1)	1	0	0	0	0
Arrhythmia	1 (0)	0	0	1 (0)	0	0	0	0	0
Bradycardia sinus	0	0	0	1 (0)	1	0	0	0	0
Cardiovascular dis	0	0	0	1 (0)	0	0	0	0	0
Cerebrovascular disorder	1 (1)	1	0	1 (0)	1	0	0	0	0
Fibrillation atrial	1 (0)	0	0	0	0	0	0	0	0
Heart arrest	1 (0)	1	0	0	0	0	0	0	0
Hypertension	6 (2)	2	0	5 (2)	0	0	2 (1)	0	0
Hypotension	1 (0)	0	0	0	0	0	0	0	0
Infarct myocardial	1 (1)	1	0	0	0	0	1 (1)	1	0
Migraine	0	0	0	0	0	0	3 (2)	0	0
Palpitation	2 (1)	1	2	0	0	0	1 (1)	0	0
Phlebitis	1 (0)	0	0	0	0	0	0	0	0
Syncope	3 (1)	2	0	1 (0)	1	0	0	0	0
Thrombophlebitis	0	0	0	1 (0)	0	0	0	0	0
Vascular disorder	0	0	0	0	0	0	1 (1)	0	0
Vascular disorder peripheral	0	0	0	0	0	0	1 (1)	0	0
Vasodilation	1 (0)	0	1	2 (1)	1	0	0	0	0
Digestive system	⟨259⟩	⟨24⟩	⟨110⟩	⟨174⟩	⟨15⟩	⟨80⟩	⟨43⟩	⟨2⟩	⟨15⟩
Abdominal pain	35 (11)	5	16	29 (9)	6	13	4 (2)	0	2
Anorexia	3 (1)	0	0	0	0	0	0	0	0
Appetite increased	1 (0)	0	0	1 (0)	0	0	0	0	0
Cholelithiasis	1 (0)	0	0	0	0	0	0	0	0
Constipation	24 (7)	0	8	19 (6)	0	6	1 (1)	0	1
Diarrhea	27 (8)	3	7	21 (7)	0	5	9 (6)	0	2
Dyspepsia	54 (17)	2	33	41 (13)	3	23	8 (5)	0	4
Dysphagia	1 (0)	0	0	0	0	0	0	0	0
Eructation	3 (1)	0	1	1 (0)	0	1	0	0	0

	OxK-1200			*Ox-1200*			*Placebo*		
Subjects exposed	***N=322***			***N=320***			***N=161***		
Adverse events (by COSTART term)	***# subjects with AE***			***# subjects with AE***			***# subjects with AE***		
	N (%)	***Sev***	***Rel***	***N (%)***	***Sev***	***Rel***	***N (%)***	***Sev***	***Rel***
Esophagitis	1 (0)	0	0	2 (1)	0	1	0	0	0
Flatulence	19 (6)	2	10	12 (4)	0	10	3 (2)	0	1
Gastritis	3 (1)	1	1	4 (1)	1	4	2 (1)	0	1
Gastroenteritis	1 (0)	1	0	3 (1)	1		3 (2)	1	0
GI disorder	4 (1)	0	0	3 (1)	2	1	0	0	0
Glossitis	2(1)	0	0	0	0	0	0	0	0
Liver function abnormal	5 (2)	1	3	3 (1)	0	1	1 (1)	0	1
Melena	2 (1)	0	1	1 (0)	0	1	1 (1)	0	0
Nausea	43 (13)	5	20	20 (6)	2	10	5 (3)	0	2
Rectal disorder	1 (0)	0	0	0	0	0	0	0	0
Stomatitis	1 (0)	0	1	1 (0)	0	1	0	0	0
Stomatitis ulcerative	1 (0	0	0	0	0	0	0	0	0
Stool abnormality	2 (1)	0	0	1 (0)	0	1	0	0	0
Tooth disorder	4 (1)	0	0	5 (2)	0	0	3 (2)	1	0
Ulcer duodenum	2 (1)	2	1	0	0	0	0	0	0
Ulcer peptic	2 (1)	0	2	0	0	0	0	0	0
Ulcer stomach	3 (1)	1	2	0	0	0	0	0	0
Vomiting	14 (4)	1	4	7 (2)	0	2	3 (2)	0	1
Endocrine	⟨1⟩	⟨0⟩	⟨0⟩	⟨1⟩	⟨0⟩	⟨0⟩	⟨2⟩	⟨0⟩	⟨0⟩
Diabetes mellitus	0	0	0	1 (0)	0	0	1 (1)	0	0
Hypothyroidism	1 (0)	0	0	0	0	0	1 (1)	0	0
Hemic & lymphatic	⟨32⟩	⟨1⟩	⟨1⟩	⟨21⟩	⟨1⟩	⟨0⟩	⟨3⟩	⟨0⟩	⟨0⟩
Anemia	14 (4)	1	0	11 (3)	1	0	1 (1)	0	0
Leucocytosis	2 (1)	0	0	0	0	0	0	0	0
Leucopenia	7 (2)	0	1	2 (1)	0	0	1 (1)	0	0
Lymphadenopathy	1 (0)	0	0	0	0	0	0	0	0
Lymphangitis	1 (0.3)	0	0	0	0	0	0	0	0
Purpura	6 (2)	0	0	6 (2)	0	0	0	0	0
Thrombocythemia	1 (0)	0	0	1 (0)	0	0	1 (1)	0	0

	OxK-1200			*Ox-1200*			*Placebo*		
Subjects exposed	***N=322***			***N=320***			***N=161***		
Adverse events (by COSTART term)	***# subjects with AE***			***# subjects with AE***			***# subjects with AE***		
	N (%)	***Sev***	***Rel***	***N (%)***	***Sev***	***Rel***	***N (%)***	***Sev***	***Rel***
Thrombocytopenia	0	0	0	1 (0)	0	0	0	0	0
Metabolic & nutritional	⟨76⟩	⟨2⟩	⟨30⟩	⟨94⟩	⟨3⟩	⟨17⟩	⟨16⟩	⟨0⟩	⟨1⟩
Bilirubinemia	1 (0)	0	0	2 (1)	0	0	0	0	0
BUN increased	8 (2)	0	1	7 (2)	0	3	1 (1)	0	0
Dehydration	1 (1)	0	0	0	0	0	0	0	0
Edema	0	0	0	5 (2)	0	0	1 (1)	0	0
Edema general	0	0	0	0	0	0	1 (0)	0	0
Edema peripheral	6 (2)	0	0	5 (2)	1	0	2 (1)	0	0
Electrolyte abnormality	0	0	0	1 (0)	0	0	0	0	0
Gout	0	0	0	0	0	0	1 (1)	0	0
Glycosuria	3 (1)	0	0	2 (1)	0	0	1 (1)	0	0
Hyperglycemia	2 (1)	2	0	1 (0)	0	0	0	0	0
Hyperlipemia	0	0	0	1 (0)	0	0	0	0	0
Hypochloremia	1 (0)	0	0	1 (0)	0	0	0	0	0
Hypokalemia	1 (0)	0	0	2 (1)	0	0	4 (2)	0	0
Hyponatremia	5 (2)	0	1	2 (1)	0	0	1 (1)	0	0
NPN increased	7 (2)	0	3	9 (3)	0	4	2 (1)	0	1
Phosphatase alkaline inc	2 (1)	0	1	1 (0)	0	0	0	0	0
SGOT increased	20 (6)	0	13	11 (3)	1	5	0	0	0
SGPT increased	18 (6)	0	11	13 (4)	1	5	2 (1)	0	0
Weight increase	1 (0)	0	0	1 (0)	0	0	0	0	0
Musculoskeletal system	⟨29⟩	⟨5⟩	⟨1⟩	⟨32⟩	⟨7⟩	⟨1⟩	⟨21⟩	⟨7⟩	⟨0⟩
Arthralgia	15 (5)	2	1	15 (5)	2	1	10 (6)	4	0
Arthritis	3 (2)	2	0	3 (1)	1	0	3 (2)	2	0
Arthrosis	4 (1)	0	0	2 (1)	2	0	0	0	0
Bone disorder	1 (0)	0	0	0	0	0	0	0	0
Bone fracture spontaneous	1 (0)	0	0	4 (1)	0	0	2 (1)	1	0
Myalgia	0	0	0	1 (0)	0	0	2 (1)	0	0
Myasthenia	0	0	0	1 (0)	0	0	0	0	0

	OxK-1200			*Ox-1200*			*Placebo*		
Subjects exposed	***N=322***			***N=320***			***N=161***		
Adverse events (by COSTART term)	***# subjects with AE***			***# subjects with AE***			***# subjects with AE***		
	N (%)	***Sev***	***Rel***	***N (%)***	***Sev***	***Rel***	***N (%)***	***Sev***	***Rel***
Myositis	0	0	0	0	0	0	1 (1)	0	0
Synovitis	2 (1)	1	0	5 (2)	2	0	2 (1)	0	0
Tendon disorder	1 (0)	0	0	0	0	0	0	0	0
Tenosynovitis	2 (1)	0	0	1 (0)	0	0	1 (1)	0	0
Nervous system	⟨48⟩	⟨4⟩	⟨3⟩	⟨59⟩	⟨5⟩	⟨4⟩	⟨21⟩	⟨3⟩	⟨0⟩
Amnesia	0	0	0	1 (0)	0	0	0	0	0
Anxiety	2 (1)	0	0	3 (1)	0	0	2 (1)	0	0
Ataxia	0	0	0	1 (0)	0	1	0	0	0
Cramps leg	6 (2)	3	0	4 (1)	2	0	1 (1)	0	0
Depersonalization	0	0	0	1 (0)	0	0	0	0	0
Depression	4 (1)	0	0	5 (2)	0	0	3 (2)	0	0
Dizziness	11 (3)	0	2	14 (4)	1	3	5 (3)	1	0
Emotional lability	2 (1)	0	0	2 (1)	0	0	1 (1)	0	0
Gait abnormal	0	0	0	1 (0)	0	0	0	0	0
Hyperkinesia	0	0	0	1 (0)	0	0	0	0	0
Hypertonia	2 (1)	0	0	5 (2)	1	0	1 (1)	0	0
Hypesthesia	2 (1)	0	0	0	0	0	1 (1)	0	0
Insomnia	2 (1)	0	0	5 (2)	0	0	3 (2)	1	0
Nervousness	4 (1)	1	0	5 (2)	0	0	0	0	0
Neuralgia	1 (0)	0	0	1 (0)	0	0	1 (1)	1	0
Neuropathy	1 (0)	0	0	0	0	0	0	0	0
Somnolence	6 (2)	0	0	6 (2)	1	0	2 (1)	0	0
Thinking abnormal	0	0	0	1 (0)	0	0	0	0	0
Tremor	1 (0)	0	0	0	0	0	0	0	0
Twitch	0	0	0	1 (0)	0	0	0	0	0
Vertigo	4 (1)	0	1	2 (1)	0	0	1 (1)	0	0
Respiratory system	⟨98⟩	⟨11⟩	⟨0⟩	⟨85⟩	⟨3⟩	⟨0⟩	⟨33⟩	⟨1⟩	⟨1⟩
Asthma	1 (0)	0		1 (0)	1		1 (1)	0	
Bronchitis	7 (2)	1		7 (2)	1		4 (2)	1	

	OxK-1200			*Ox-1200*			*Placebo*		
Subjects exposed	***N=322***			***N=320***			***N=161***		
Adverse events (by COSTART term)	***# subjects with AE***			***# subjects with AE***			***# subjects with AE***		
	N (%)	***Sev***	***Rel***	***N (%)***	***Sev***	***Rel***	***N (%)***	***Sev***	***Rel***
Cough increased	16 (5)	3		4 (1)	0		3 (2)	0	
Dyspnea	4 (1)	0		3 (1)	0		0		
Edema lung	0	0	0	1 (0)	0	0	0	0	0
Emphysema	1 (0)	0	0	0	0	0	0	0	0
Epistaxis	2 (1)	1	0	1 (0)	0	0	0	0	0
Laryngitis	2 (1)	0	0	0	0	0	0	0	0
Nasal septum disorder	0	0	0	0	0	0	1 (1)	0	1
Pharyngitis	38 (12)	3	0	43 (13)	0	0	14 (9)	0	0
Pneumonia	3 (1)	2	0	1 (0)	0	0	0	0	0
Respiratory disorder	3 (1)	1	0	1 (0)	1	0	1 (1)	0	0
Rhinitis	8 (2)	0	0	9 (3)	0	0	3 (2)	0	0
Sinusitis	11 (3)	0	0	14 (4)	0	0	6 (4)	0	0
Voice alteration	2 (1)	0	0	0	0	0	0	0	0
Skin & appendages	⟨29⟩	⟨4⟩	⟨4⟩	⟨20⟩	⟨1⟩	⟨3⟩	⟨8⟩	⟨0⟩	⟨3⟩
Acne	2 (1)	0	0	0	0	0	0	0	0
Alopecia	2 (1)	0	0	0	0	0	0	0	0
Dermatitis contact	3 (1)	0	0	0	0	0	0	0	0
Dermatitis fungal	1 (0)	0	0	0	0	0	0	0	0
Dermatitis lichenoid	1 (0)	0	0	0	0	0	0	0	0
Furunculosis	1 (0)	0	0	0	0	0	0	0	0
Herpes simplex	0	0	0	1 (0)	0	0	1 (1)	0	0
Herpes zoster	2 (1)	0	0	0	0	0	0	0	0
Nail disorder	1 (0)	0	0	1 (0)	0	0	0	0	0
Photosensitivity	0	0	0	1 (0)	0	0	0	0	0
Pruritus	1 (0)	1	0	1 (0)	1	0	4 (2)	0	1
Psoriasis	1 (0)	0	0	1 (0)	0	0	0	0	0
Rash	12 (4)	3	4	11 (3)	0	2	1 (1)	0	0
Seborrhea	0	0	0	1 (0)	0	0	0	0	0
Skin disorder	1 (0)	0	0	1 (0)	0	0	0	0	0

	OxK-1200			*Ox-1200*			*Placebo*		
Subjects exposed	***N=322***			***N=320***			***N=161***		
Adverse events (by COSTART term)	***# subjects with AE***			***# subjects with AE***			***# subjects with AE***		
	N (%)	***Sev***	***Rel***	***N (%)***	***Sev***	***Rel***	***N (%)***	***Sev***	***Rel***
Sweating	1 (0)	0	0	1 (0)	0	0	1 (1)	0	1
Urticaria	0	0	0	1 (0)	0	1	1 (1)	0	1
Special senses	⟨17⟩	⟨0⟩	⟨4⟩	⟨18⟩	⟨1⟩	⟨4⟩	⟨7⟩	⟨0⟩	⟨0⟩
Cataract	1 (0)	0	0	1 (0)	0	0	0	0	0
Conjunctivitis	0	0	0	2 (1)	0	0	1 (1)	0	0
Ear disorder	3 (1)	0	0	1 (0)	0	0	1 (1)	0	0
Glaucoma	0	0	0	1 (0)	0	1	0	0	0
Otitis media	3 (1)	0	0	1 (0)	0	0	2 (1)	0	0
Pain ear	2 (1)	0	0	1 (0)	0	0	1 (1)	0	0
Pain eye	0	0	0	0		0	1 (1)	0	0
Retinal detachment	0	0	0	1 (0)	0	0	0	0	0
Taste perversion	2 (1)	0	1	1 (0)	0	0	0	0	0
Tinnitus	3 (1)	0	1	8 (3)	1	3	0	0	0
Ulcer corneal	1 (0)	0	0	0	0	0	0	0	0
Vision abnormal	2 (1)	0	2	1 (0)	0	0	1 (1)	0	0
Urogenital system	⟨25⟩	⟨1⟩	⟨1⟩	⟨32⟩	⟨2⟩	⟨0⟩	⟨15⟩	⟨1⟩	⟨0⟩
Albuminuria	1 (0)	0	0	2 (1)	0	0	3 (2)	0	0
Cystitis	0	0	0	1 (0)	0	0	0	0	0
Dysmenorrhea	0	0	0	0	0	0	1 (1)	0	0
Hemorrhage vaginal	1 (0)	0	0	0	0	0	0	0	0
Hematuria	8 (2)	0	0	5 (2)	0	0	3 (2)	0	0
Impotence	0	0	0	1 (0)	0	0	0	0	0
Incontinence urinary	1 (0)	0	0	0	0	0	0	0	0
Infection urinary tract	7 (2)	0	0	9 (3)	0	0	4 (2)	0	0
Kidney calculus	0	0	0	1 (1)	0	0	0	0	0
Metrorrhagia	0	0	0	1 (0)	0	0	0	0	0
Neoplasm breast	0	0	0	2 (1)	1	0	2 (1)	1	0
Pain breast	0	0	0	1 (0)	0	0	0	0	0
Pain pelvic	0	0	0	1 (0)	0	0	0	0	0

	OxK-1200			***Ox-1200***			***Placebo***		
Subjects exposed	***N=322***			***N=320***			***N=161***		
Adverse events (by COSTART term)	***# subjects with AE***			***# subjects with AE***			***# subjects with AE***		
	N (%)	***Sev***	***Rel***	***N (%)***	***Sev***	***Rel***	***N (%)***	***Sev***	***Rel***
PAP smear suspicious	0	0	0	1 (0)	0	0	0	0	0
Prostatic disorder	1 (0)	1	0	1 (0)	0	0	1 (1)	0	0
Pyelonephritis	1 (0)	0	0	2 (1)	1	0	0	0	0
Urine abnormality	4 (1)	0	1	3 (1)	0	0	1 (1)	0	0
Urinary frequency	1 (0)	0	0	0	0	0	0	0	0
Urinary tract disorder	0	0	0	1 (1)	0	0	0	0	0

Table 2. Inventory of the post-marketing clinical studies of Daypro

Report Number	Study Design	Study Duration	Treatment Groups	Number of Patients in Treatment Group
SINGLE DOSE PHARMACOKINETIC AND DENTAL PAIN STUDIES				
S65-94-06-015	Single-center, randomized double-blind, placebo-controlled, parallel group, single dose study of patients with pain after tooth extractions	Each treatment had a single dose.	Oxaprozin Acid 1800 mg Placebo	24 8
S65-94-06-020	Single-center, open label, randomized, two-treatment, two-period, single-dose drug crossover study in normal subjects	Each treatment period had a single dose	Oxaprozin Acid (Treatment A) 600 mg Oxaprozin Acid (Treatment B) 600 mg	18
S65-95-06-027	Single-center, open label, randomized, three-dose, three period, single dose crossover study in healthy volunteers	Each treatment period had a single dose	Oxaprozin Acid 600 mg Oxaprozin Acid 1200 mg Oxaprozin Acid 1800 mg	38
MULTIPLE DOSE PHARMACOKINETIC STUDIES (<4 WEEKS)				
S65-95-06-013	Single-center, open label, two-dose regimen, rising dose pharmacokinetic and pharmacodynamic study in OA patients with and without renal impairment	Each treatment had a single dose (1 day) and multiple dose (22 days) portions	Oxaprozin Acid 600 mg QD Oxaprozin Acid 1200 mg QD	42
S65-95-06-016	Multi-center, randomized, double-blind, parallel group study of patients with acute soft tissues injuries	4-7 days	Oxaproxin Acid 1200 mg QD Naproxen 500 mg BID	4 4
S65-95-06-017	Single-center, open label, two treatment, three period, multiple dose drug interaction study in normal subjects	Each treatment period was 7 days	Lithium Carbonate 450 mg BID Lithium Carbonate 450 mg BID and Oxaprozin Acid 1200 mg QD Oxaprozin Acid 1200 mg QD	20
S65-95-06-023	Single-center, open label, multiple dose, single treatment, sequence interaction study in subjects with Type II non-insulin dependent diabetes mellitus	Glyburide alone for 1 day then co-administration for 7 days	Glyburide 5 mg or 10 mg QD and Oxaprozin Acid 1200 mg QD	17
N65-95-06-025	Multi-center, open label, multiple dose interaction study in patients with RA	Methotrexate alone, then 7 days of Oxaprozin ending with co-administration with next weekly Methotrexate dose	Methotrexate Methotrexate and Oxaprozin Acid 1200 mg QD	18
N65-95-06-026	Multi-center, open label, multiple dose interaction study in patients with mild to moderate hypertension	Enalpril alone, then 21 to 28 days of Oxaprozin co-administration	Enalpril 10 mg, 20 mg or 40 mg QAM and Oxaprozin Acid 1200 mg QD	27
S65-95-06-028	Single-center, open label, multiple dose study in healthy volunteers	8 days	Oxaprozin Acid 1800 mg QD	25
S65-96-06-029	Single-center, open label, randomized, placebo-controlled study of platelet function in normal subjects	8 days	Oxaprozin Acid 1200 mg QD Placebo	15 6
MULTIPLE DOSE OSTEOARTHRITIS STUDIES (≥ 4 WEEKS)				
S65-94-06-004	Single-center, open label, randomized, two-treatment, two period, crossover, pharmacokinetic and pharmacodynamic study in healthy, young and elderly OA subjects; An open label extension study in elderly OA patients followed the crossover portion of the study.	Each treatment had a single dose (1 day) and multiple dose (22 days) portions 8 weeks	Oxaprozin Acid 1200 mg QD Piroxicam 20 mg QD Oxaprozin Acid 1200 mg	54 22
S65-94-06-009	Multi-center, randomized, double-blind, placebo-controlled, parallel group study of patients with OA of the knee	6 weeks	Oxaprozin Acid 1200 mg QD Naproxen 500 mg BID Placebo	90 89 56
S65-94-06-010	Multi-center randomized, double-blind, parallel group study of patients with OA of the knee	4 weeks	Oxaprozin Acid 600 mg TID Naproxen 500 mg TID	82 84
S65-95-06-021	Multi-center, randomized, double-blind placebo-controlled, parallel group study of patients with OA of the knee	6 weeks	Oxaprozin Acid 1200 mg QD Nabumetone 1000 mg QD Placebo	109 110 109
S65-95-06-022	Multi-center, randomized, double-blind, placebo-controlled parallel group study of patients with OA of the knee	6 weeks	Oxaprozin Acid 1200 mg QD Nabumetone 1500 mg QD Placebo	116 115 116

Table 3a. Single Dose Pharmacokinetic and Dental Pain Studies Individual Adverse Events (%)

study number	015 (b)	013		020		027			total
BODY SYSTEM	1800 mg	600 mg	1200 mg	1200 mg form A	1200 mg form B	600 mg	1200 mg	1800 mg	
no. of patients	n = 24	n = 42	n = 42	n = 18	n = 18	n = 38	n = 38	n = 38	n = 258
Gastrointestinal									
Nausea	4 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5%)	6 (2%)
Central and Peripheral Nervous									
Dizziness	4 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	1 (3%)	6 (2%)
Body as a Whole									
Pain	6 (26%)	1 (2%)	0 (0%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	8 (3%)
Headache	0 (0%)	3 (7%)	1 (2%)	1 (6%)	3 (17%)	0 (0%)	0 (0%)	1 (3%)	9 (3%)
ANY ADVERSE EVENT	11 (48%)	11 (26%)	4 (10%)	4 (22%)	5 (28%)	7 (18%)	5 (13%)	10 (26%)	57 (22%)

(a) Adverse events reported by more than two subjects/patients in a given treatment group. Single dose adverse event data for Study 004 was combined with multiple dose PK data in Table 6.
(b) Dental Pain Study

Table 3b. Multiple Dose Pharmacokinetic Studies of Less than Four Weeks in Duration Individual Adverse Events (%)

STUDY NUMBER	016	017	023	025	028	029	013		004	026	total
DOSE	1200 mg	1200 mg	1200 mg	1200 mg	1800 mg	1200 mg	600 mg	1200 mg	1200 mg	1200 mg	
DURATION	qd 4-7 days	qd (b) 7 days	qd (c) 7 days	QD (d) 7 days	qd 8 days	qd 8 days	qd 22 days	qd 22 days	qd (e) 22 days	qd (f) 1-29 days	
NO. OF PATIENTS	n = 4	n = 20	n = 8	n = 18	n = 25	n = 15	n = 42	n = 42	n = 54	n = 27	N = 255
Gastrointestinal											
Dyspepsia	0 (0%)	0 (0%)	1 (13%)	1 (6%)	5 (20%)	0 (0%)	2 (5%)	0 (0%)	0 (0%)	2 (7%)	11 (4%)
Nausea	0 (0%)	1 (5%)	2 (25%)	2 (11%)	6 (24%)	1 (7%)	2 (5%)	1 (2%)	2 (4%)	1 (4%)	18 (7%)
Diarrhea	0 (0%)	2 (10%)	2 (25%)	1 (6%)	3 (12%)	1 (7%)	2 (5%)	1 (2%)	0 (0%)	2 (7%)	14 (5%)
Constipation	0 (0%)	0 (0%)	2 (25%)	0 (0%)	3 (12%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)	7 (3%)
Body as a Whole											
Headache	1 (25%)	5 (25%)	4 (50%)	6 (33%)	10 (40%)	0 (0%)	0 (0%)	2 (5%)	5 (9%)	6 (22%)	39 (15%)
Musculoskeletal											
Arthralgia	0 (0%)	0 (0%)	0 (0%)	3 (17%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (2%)
Liver and Biliary											
SGOT Increased	0 (0%)	4 (20%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	6 (2%)
SGPT Increased	0 (0%)	5 (25%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (2%)
Red Blood Cell											
Anemia	0 (0%)	3 (15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	3 (7%)	0 (0%)	0 (0%)	7 (3%)
ANY ADVERSE EVENT	2 (50%)	15 (75%)	8 (100%)	11 (61%)	17 (68%)	4 (27%)	16 (38%)	20 (48%)	12 (22%)	16 (59%)	121 (47%)

(a) Individual adverse events reported by more than two subjects in a given treatment group
(b) Oxaprozin alone
(c) Oxaprozin + 10 mg glyburide BID
(d) Oxaprozin + ≤20 mg methotrexate/week
(e) Combined treatment emergent adverse events from both single and multiple dose PK phases
(f) Oxaprozin + enalapril

Table 3c. Multiple Dose Osteoarthritis Studies of Four Weeks or More in Duration Individual Adverse Events (%)

study number	009	010	021	022	004	total
dose DURATION	1200 mg qd 6 weeks	600 mg tid 4 weeks	1200 mg qd 6 weeks	1200 mg qd 6 weeks	1200 mg qd 8 WEEKS	
no. of patients	N = 90	n = 82	n = 109	n = 116	N = 22	n = 419
Gastrointestinal						
Abdominal Pain	11 (12%)	13 (16%)	10 (9%)	12 (10%)	0 (0%)	46 (11%)
Dyspepsia	7 (8%)	14 (17%)	9 (8%)	11 (9%)	0 (0%)	41 (10%)
Nausea	5 (6%)	16 (20%)	9 (8%)	9 (8%)	0 (0%)	39 (9%)
Diarrhea	6 (7%)	6 (7%)	6 (6%)	3 (3%)	0 (0%)	21 (5%)
Flatulence	5 (6%)	1 (1%)	4 (4%)	2 (2%)	0 (0%)	12 (3%)
Constipation	3 (3%)	4 (5%)	10 (9%)	5 (4%)	0 (0%)	22 (5%)
Melena	2 (2%) (b)	2 (2%) (b)	1 (1%) (b)	4 (3%) (c)	0 (0%)	9 (2%)
Respiratory						
Upper Resp Infect	9 (10%)	12 (15%)	2 (2%)	3 (3%)	1 (5%)	27 (6%)
Rhinitis	3 (3%)	3 (4%)	1 (<1%)	11 (9%)	0 (0%)	18 (4%)
Coughing	6 (7%)	1 (1%)	1 (<1%)	8 (7%)	0 (0%)	16 (4%)
Pharyngitis	3 (3%)	2 (2%)	1 (<1%)	6 (5%)	0 (0%)	12 (3%)
Central and Peripheral Nervous						
Headache	12 (13%)	9 (11%)	12 (11%)	6 (5%)	0 (0%)	39 (9%)
Dizziness	5 (6%)	2 (2%)	4 (4%)	5 (4%)	0 (0%)	16 (4%)
Body as a Whole						
Injury - Accidental	3 (3%)	1 (1%)	5 (5%)	1 (<1%)	0 (0%)	10 (2%)
Metabolic and Nutritional						
Diabetes Aggravated	5 (6%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	6 (1%)
Skin and Appendages						
Pruritus	5 (6%)	1 (1%)	1 (<1%)	2 (2%)	0 (0%)	9 (2%)
Liver and Biliary System						
Hepatic Function Abn	2 (2%)	1 (1%)	5 (5%)	0 (0%)	0 (0%)	8 (2%) (d)
ANY ADVERSE EVENT	61 (68%)	64 (78%)	71 (65%)	83 (72%)	5 (23%)	284 (68%)

(a) Adverse events occurring in ≥5% of patients in a given treatment group
(b) Positive Hemoccults
(c) Positive Hemoccults for two patients
(d) Seven patients also had increased SGOT and SGPT but were not included in table as only events occurring in >5% in at least one study have been included

Table 4. Marketing Experience With Oxaprozin (Daypro®)

DRUG EXPERIENCE REPORTING SYSTEM
Frequency Analysis

Product: DAYPRO (33,501/18-841) OCT-29-1992 to OCT-28-1996

Body System Event Terms	United States Spontaneous		Body System Total	
Gastro-Intestinal System Disorders			600	*132*
DYSPEPSIA	98	*4*		
NAUSEA	88	*5*		
ABDOMINAL PAIN	86	*8*		
GI HEMORRHAGE	58	*38*		
DIARRHEA	41	*3*		
CONSTIPATION	36	*2*		
GASTROINTESTINAL DISTURBANCE	29	*6*		
VOMITING	22	*5*		
STOMATITIS	17	*3*		
MELENA	15	*5*		
HEMORRHAGE RECTUM	13	*2*		
PANCREATITIS	9	*8*		
GASTRITIS	9	*4*		
FLATULENCE	9			
DUODENAL ULCER HEMORRHAGIC	7	*7*		
STOMATITIS ULCERATIVE	6	*2*		
PEPTIC ULCER	5	*3*		
GASTRIC ULCER HEMORRHAGIC	4	*4*		
HEMATEMESIS	4	*2*		
PEPTIC ULCER HEMORRHAGIC	4	*2*		
DUODENAL ULCER	3	*2*		
DYSPHAGIA	3	*1*		
ESOPHAGITIS	3	*1*		
FECES DISCOLORED	3			
GASTRITIS HEMORRHAGIC	2	*2*		
ESOPHAGEAL ULCERATION	2	*2*		
TONGUE EDEMA	2	*1*		
GASTROESOPHAGEAL REFLUX	2	*1*		
GLOSSITIS	2			
HICCUP	2			
TONGUE DISCOLORATION	2			
COLITIS	1	*1*		
DUODENAL ULCER PERFORATED	1	*1*		
GASTROENTERITIS	1	*1*		
INTESTINAL GANGRENE	1	*1*		
INTESTINAL OBSTRUCTION	1	*1*		
PEPTIC ULCER HEMPER	1	*1*		
PEPTIC ULCER PERFORATED	1	*1*		
ILEITIS AGGRAVATED	1	*1*		
DIVERTICULITIS	1	*1*		
PEPTIC ULCER AGGRAVATED	1			
ERUCTATION	1			
GASTRIC ULCER	1			
TOOTH DISORDER	1			
STOOLS ABNORMAL	1			

DRUG EXPERIENCE REPORTING SYSTEM
Frequency Analysis

Product: DAYPRO (33,501/18-841) OCT-29-1992 to OCT-28-1996

Body System Event Terms	United States Spontaneous		Body System Total	
Body as a Whole - General Disorders			494	*68*
THERAPEUTIC RESPONSE DECREASED	108	*2*		
ALLERGIC REACTION	67	*15*		
LABORATORY TEST ABNORMAL	47	*2*		
EDEMA	38	*6*		
UNSPECIFIED EXPERIENCE	35	*1*		
ANAPHYLACTOID REACTION	23	*11*		
FEVER	23	*5*		
FATIGUE	22	*1*		
MALAISE	21	*2*		
FACE EDEMA	20	*2*		
ASTHENIA	14	*3*		
RIGORS	14	*1*		
CHEST PAIN	11	*1*		
UNEXPECTED THERAPEUTIC EFFECT	8			
HOT FLUSHES	7	*2*		
INFLUENZA-LIKE SYMPTOMS	7	*1*		
SERUM SICKNESS	5	*4*		
OVERDOSE	5	*3*		
DRUG INTERACTION NOS	5	*2*		
PAIN	4			
EDEMA PERIPHERAL	2			
BACK PAIN	2			
EDEMA GENERALIZED	1	*1*		
ANAPHYLACTIC SHOCK	1	*1*		
SERUM DRUG LEVEL INCREASED	1	*1*		
INJURY-ACCIDENTAL	1	*1*		
ESR INCREASED	1			
CRYING ABNORMAL	1			

DRUG EXPERIENCE REPORTING SYSTEM
Frequency Analysis

Product: DAYPRO (33,501/18-841) OCT-29-1992 to OCT-28-1996

Body System Event Terms	United States Spontaneous		Body System Total	
Skin and Appendages Disorders			411	*56*
RASH	104	*8*		
PRURITUS	54	*5*		
URTICARIA	40	*4*		
ALOPECIA	38	*2*		
PHOTOSENSITIVITY REACTION	25	*2*		
RASH MACULO-PAPULAR	20	*1*		
BULLOUS ERUPTION	20	*1*		
RASH ERYTHEMATOUS	14	*3*		
STEVENS JOHNSON SYNDROME	12	*10*		
DERMATITIS EXFOLIATIVE	11	*4*		
ANGIOEDEMA	10	*5*		
SKIN EXFOLIATION	10	*2*		
SWEATING INCREASED	9	*1*		
SKIN DISCOLORATION	6	*1*		
ERYTHEMA MULTIFORME	5	*2*		
DERMATITIS	5			
SKIN DISORDER	4			
EPIDERMAL NECROLYSIS	3	*3*		
NAIL DISORDER	3			
RASH PSORIAFORM	3			
SKIN COLD CLAMMY	3			
SKIN ULCERATION	2	*1*		
ECZEMA	2			
SKIN DRY	2			
PEMPHIGOID REACTION	1	*1*		
PHOTOSENSITIVITY ALLERGIC REACT	1			
RASH PUSTULAR	1			
SKIN HYPERTROPHY	1			
PSORIASIS AGGRAVATED	1			
HAIR TEXTURE ABNORMAL	1			

DRUG EXPERIENCE REPORTING SYSTEM
Frequency Analysis

Product: DAYPRO (33,501/18-841) OCT-29-1992 to OCT-28-1996

Body System Event Terms	United States Spontaneous		Body System Total	
Psychiatric Disorders			172	*18*
SOMNOLENCE	30			
CONFUSION	25	*3*		
DEPRESSION	17			
INSOMNIA	16	*1*		
NERVOUSNESS	13	*2*		
AMNESIA	12	*1*		
ANOREXIA	11	*4*		
ANXIETY	10			
IMPOTENCE	7			
PARONIRIA	5	*1*		
HALLUCINATION	4	*2*		
AGITATION	3			
DEPRESSION AGGRAVATED	3			
DREAMING ABNORMAL	3			
SUICIDAL IDEATION	3			
APPETITE INCREASED	2	*1*		
EMOTIONAL LABILITY	2			
DELIRIUM	1	*1*		
AGGRESSIVE REACTION	1	*1*		
DELUSION	1	*1*		
DEPERSONALIZATION	1			
LIBIDO DECREASED	1			
THINKING ABNORMAL	1			
Central and Peripheral Nervous System Disorders			159	*11*
DIZZINESS	42	*2*		
HEADACHE	35	*2*		
PARESTHESIA	21	*1*		
TREMOR	12	*1*		
HYPOESTHESIA	10			
VERTIGO	7			
SPEECH DISORDER	4	*1*		
TWITCHING	3	*1*		
CONVULSIONS	3			
SENSORY DISTURBANCE	3			
GAIT ABNORMAL	2			
PARALYSIS	2			
CRAMPS LEGS	2			
COMA	1	*1*		
ENCEPHALOPATHY	1	*1*		
HYPERTENSION INTRACRANIAL	1	*1*		
DYSTONIA	1			
HYPERTONIA	1			
MIGRAINE	1			
NEURALGIA	1			
NEURITIS	1			
PTOSIS	1			
SCOTOMA	1			
STUPOR	1			
MENINGITIS	1			
MYASTHENIA GRAVIS-LIKE SYNDROME	1			

DRUG EXPERIENCE REPORTING SYSTEM
Frequency Analysis

Product: DAYPRO (33,501/18-841) OCT-29-1992 to OCT-28-1996

Body System Event Terms	United States Spontaneous		Body System Total	
Urinary System Disorders			80	*18*
RENAL FAILURE ACUTE	14	*8*		
HEMATURIA	14			
DYSURIA	12			
MICTURITION FREQUENCY	11	*1*		
NEPHRITIS INTERSTITIAL	4	*3*		
NEPHROSIS	3	*2*		
RENAL PAIN	3			
URINE ABNORMAL	3			
ALBUMINURIA	2	*1*		
RENAL FUNCTION ABNORMAL	2	*1*		
URINARY TRACT INFECTION	2	*1*		
MICTURITION DISORDER	2			
OLIGURIA	2			
RENAL CALCULUS	1	*1*		
URINARY RETENTION	1			
BLADDER CALCULUS	1			
NEPHRITIS	1			
POLYURIA	1			
RENAL ABSCESS	1			
Metabolic and Nutritional Disorders			77	*15*
WEIGHT INCREASE	14			
HYPERGLYCEMIA	12	*1*		
WEIGHT DECREASE	7	*2*		
HYPOGLYCEMIA	7			
CREATINE PHOSPHOKINASE INCREASED	6	*2*		
EDEMA LEGS	6	*1*		
XEROPHTHALMIA	5	*2*		
NPN INCREASED	4	*1*		
HYPERCHOLESTEROLEMIA	4			
BUN INCREASED	3	*3*		
HYPOKALEMIA	2	*2*		
LDH INCREASED	2			
DEHYDRATION	1	*1*		
ACIDOSIS	1			
HYPERCALCEMIA	1			
HYPERLIPEMIA	1			
HYPOVITAMINOSIS	1			
None			77	*1*
NO ADVERSE REACTION	77	*1*		
Platelet, Bleeding & Clotting Disorders			74	*18*
PURPURA	36	*4*		
THROMBOCYTOPENIA	18	*8*		
BLEEDING TIME INCREASED	7	*2*		
EPISTAXIS	5	*1*		
PROTHROMBIN INCREASED	2			
GINGIVAL BLEEDING	2			
COAGULATION DISORDER	1	*1*		
PROTHROMBIN DECREASED	1	*1*		
DIC	1	*1*		
HEMORRHAGE NOS	1			

DRUG EXPERIENCE REPORTING SYSTEM
Frequency Analysis

Product: DAYPRO (33,501/18-841) OCT-29-1992 to OCT-28-1996

Body System Event Terms	United States Spontaneous		Body System Total	
Liver and Biliary System Disorders			70	*21*
HEPATIC FUNCTION ABNORMAL	24	*7*		
PORPHYRIA	18			
HEPATITIS	15	*7*		
JAUNDICE	5	*2*		
HEPATIC FAILURE	2	*2*		
SGOT INCREASED	2	*1*		
CHOLECYSTITIS	1	*1*		
GALL BLADDER DISORDER	1	*1*		
HEPATITIS CHOLESTATIC	1			
SGPT INCREASED	1			
Autonomic Nervous System Disorders			55	*11*
HYPERTENSION	24	*2*		
SYNCOPE	12	*3*		
HYPOTENSION	8	*4*		
MOUTH DRY	4	*1*		
SALIVA INCREASED	3			
PALLOR	1	*1*		
MYDRIASIS	1			
GLAUCOMA	1			
HYPERTENSION AGGRAVATED	1			
Respiratory System Disorders			48	*13*
DYSPNEA	18	*5*		
LARYNGISMUS	7	*2*		
RHINITIS	5			
BRONCHOSPASM	4	*1*		
LARYNX EDEMA	3	*2*		
UPPER RESP TRACT INFECTION	2	*1*		
SINUSITIS	2			
PNEUMONIA	1	*1*		
SPUTUM INCREASED	1	*1*		
HEMOPTYSIS	1			
HYPERVENTILATION	1			
PULMONARY EDEMA	1			
RESPIRATORY DISORDER	1			
BRONCHITIS	1			
Vision Disorders			40	2
VISION ABNORMAL	22	*2*		
DIPLOPIA	4			
CONJUNCTIVITIS	3			
EYE ABNORMALITY	2			
BLINDNESS	1			
CATARACT	1			
CORNEAL OPACITY	1			
KERATITIS	1			
PHOTOPHOBIA	1			
LACRIMATION ABNORMAL	1			
CORNEAL DEPOSITS	1			
MACULA LUTEA DEGENERATION	1			
CONJUNCTIVAL HEMORRHAGE	1			

DRUG EXPERIENCE REPORTING SYSTEM
Frequency Analysis

Product: DAYPRO (33,501/18-841) OCT-29-1992 to OCT-28-1996

Body System Event Terms	United States Spontaneous		Body System Total	
White Cell and RES Disorders			34	*16*
LEUKOPENIA	19	*7*		
EOSINOPHILIA	7	*5*		
AGRANULOCYTOSIS	3	*3*		
LYMPHADENOPATHY	3	*1*		
LEUKOCYTOSIS	1			
LYMPHADENOPATHY CERVICAL	1			
Hearing and Vestibular Disorders			33	*2*
TINNITUS	23	*1*		
DEAFNESS	9	*1*		
EAR ABNORMALITY	1			
Red Blood Cell Disorders			24	*13*
ANEMIA	13	*6*		
PANCYTOPENIA	6	*4*		
MARROW DEPRESSION	2	*2*		
ANEMIA APLASTIC	1	*1*		
HEMOLYSIS	1			
IRON METABOLISM DISORDER	1			
Musculo-Skeletal System Disorders			23	*7*
ARTHRALGIA	10	*1*		
MYALGIA	6	*2*		
ARTHRITIS AGGRAVATED	3			
MYOPATHY	2	*2*		
ARTHRITIS	1	*1*		
HEMARTHROSIS	1	*1*		
Heart Rate and Rhythm Disorders			23	*3*
PALPITATION	11			
TACHYCARDIA	5			
CARDIAC ARREST	2	*2*		
FIBRILLATION ATRIAL	2	*1*		
ARRHYTHMIA VENTRICULAR	2			
ARRHYTHMIA	1			
Special Senses Other, Disorders			22	*3*
TASTE PERVERSION	16	*1*		
TASTE LOSS	4	*1*		
PAROSMIA	2	*1*		
Reproductive Disorders, Female			22	*1*
MENSTRUAL DISORDER	5			
VAGINAL HEMORRHAGE	4			
DRUG EXPOSURE DURING PREGNANCY	3	*1*		
LACTATION NONPUERPERAL	2			
MENORRHAGIA	2			
PERINEAL PAIN FEMALE	1			
BREAST ENLARGEMENT	1			
BREAST PAIN FEMALE	1			
DYSMENORRHEA	1			
INTERMENSTRUAL BLEEDING	1			
VAGINITIS	1			

DRUG EXPERIENCE REPORTING SYSTEM
Frequency Analysis

Product: DAYPRO (33,501/18-841) OCT-29-1992 to OCT-28-1996

Body System Event Terms	United States Spontaneous		Body System Total	
Vascular (Extracardiac) Disorders			19	*2*
FLUSHING	12			
VASCULITIS	4	*1*		
CEREBRAL HEMORRHAGE	1	*1*		
CEREBROVASCULAR DISORDER	1			
OCULAR HEMORRHAGE	1			
Cardiovascular Disorders, General			11	*3*
CARDIAC FAILURE	5	*2*		
EDEMA DEPENDENT	5			
HEART DISORDER	1	*1*		
Reproductive Disorders, Male			9	*2*
PROSTATIC DISORDER	4	*2*		
EJACULATION FAILURE	3			
EDEMA SCROTUM	1			
FERTILITY DECREASED MALE	1			
Resistance Mechanism Disorders			8	*4*
SEPSIS	4	*4*		
INFECTION VIRAL	1			
STOMATITIS APHTHOUS	1			
HERPES ZOSTER	1			
HERPES SIMPLEX	1			
Myo Endo Pericardial & Valve Disorders			4	*3*
MYOCARDIAL INFARCTION	2	*2*		
PERICARDITIS	1	*1*		
ANGINA PECTORIS	1			
Collagen Disorders			3	*3*
ARTHRITIS RHEUMATOID AGGRAVATED	1	*1*		
ANTINUCLEAR FACTOR TEST POSITIVE	1	*1*		
COLD AGGLUTININS POSITIVE	1	*1*		
Application Site Disorders			2	*1*
CELLULITIS	1	*1*		
SKIN NODULE	1			
Endocrine Disorders			2	
GYNECOMASTIA	1			
HYPOTHYROIDISM	1			
Neoplasm			1	*1*
LEUKEMIA	1	*1*		

Total Number of Events:	2597	*448*
Total Number of Reports:	1543	*212*

Table 5. Relative reporting frequency of fatal AEs for NSAIDs

Overview of Total and Fatal Reports
(descending order by total)

NSAID	# total	# fatal	Percent
Naproxen OTC	8461	14	0.2%
Ibuprofen Rx	6732	319	4.7%
Naproxen Rx	6204	351	5.7%
Ibuprofen OTC	5675	45	0.8%
Piroxicam	5441	349	6.4%
Zomepirac	5338	221	4.1%
Diclofenac Sodium	4492	651	**14.5%**
Indomethacin	4149	503	**12.1%**
Sulindac	4103	270	6.6%
Acetaminophen (single)	3466	524	**15.1%**
Benoxaprofen	3266	334	**10.2%**
Nabumetone	2637	53	2.0%
Aspirin (single)	2595	199	7.7%
Fenoprofen	2494	91	3.6%
Ketorolac IM	2283	167	7.3%
Tolmetin	2075	108	5.2%
Etodolac	1780	42	2.4%
Oxaprozin	1764	34	1.9%
Diflunisal	1458	90	6.2%
Phenylbutazone	1254	210	**16.7%**
Ketoprofen Rx	1182	57	4.8%
Ketoprofen OTC	1171	0	0.0%
Naproxen Sodium	1155	36	3.1%
Flurbiprofen Oral	1060	26	2.5%
Ketorolac Oral	903	49	5.4%
Suprofen Oral	595	10	1.7%
Sodium Meclofenamate	558	18	3.2%
Oxyphenbutazone	458	59	**12.9%**
Mefenamic Acid	386	36	9.3%
Diclofenac Potassium	242	15	6.2%
Diclofenac XR	57	30	**52.6%**

Table 6a. Incidence (%) of Most Commonly Occurring Adverse Events and Withdrawals due to Adverse Events in Published RA Trials with Oxaprozin Acid[a]

	Barber, et al [1] 6 months n=109	Vreede, et al [2] 2-6 months n=73	Appelrouth, et al [3] 6 months n=79	Poiley, et al [4] 1 year n=98
Headache	8			1
Rash	8	10	18	6
Nausea	7	12	10	5
Dyspepsia	5	10	13	3
Abdominal Pain	4	15	9	5
Constipation	5	10	8	
Diarrhea		8		5
Tinnitus	5			
Vomiting				1
Appetite Change			6	
Flatulence			6	
Withdrawal due to AE	11	16	11	15

Blank cell = not reported in the paper, AE= Adverse Event

a "Most commonly occurring" as defined by each author

Table 6b. Incidence (%) of Most Commonly Occurring Adverse Events and Withdrawals due to Adverse Events in Published OA Trials with Oxaprozin Acid[a]

	Kolodny, et al [5] 6 months n=456	Powell, et al [6] 12 weeks n=45	Weaver, et al [7] 6 weeks n=109	Makarowski, et al [8] 6 weeks n=116
Abdominal Pain	8	11	9	10
Nausea	8	13	8	8
Dyspepsia	5	9	8	9
Headache		11	11	5
Constipation	5	7	9	
Diarrhea			8	3
Flatulence			4	2
Rhinitis				9
Coughing				7
Pharyngitis				5
Insomnia			4	
Dizziness			4	
Rash	4			
Vomiting		4		
Tinnitus	3			
Withdrawal due to AE	13	20	7	9

Blank cell = not reported in the paper, AE= Adverse Event

a "Most commonly occurring" as defined by each author

2. References

(1) Barber JV, Collins RL, Kitridou RC, Lehman DH, Wenger ME, and Wold RT. The efficacy and safety of single daily doses of oxaprozin in the treatment of rheumatoid arthritis: a comparison with aspirin. Semin Arthritis Rheum 1986;15(3 suppl 2):47-53.

(2) Vreede PD, Hamer FE, and Sheldon WB. Use of oxaprozin in the treatment of aspirin failures in rheumatoid arthritis. Semin Arthritis Rheum 1986;15(3 suppl 2):66-71.

(3) Appelrouth DT, Chodock AL, Miller JL, and Powell WR. A comparison of single daily doses of oxaprozin with multiple daily doses of ibuprofen for the treatment of rheumatoid arthritis. Semin Arthritis Rheum 1986;15(3 suppl 2):54-58.

(4) Polley JE, Spindler JS, Clarke JP, and Brame CL. Nonsteroidal antiinflammatory drug therapy in rheumatoid arthritis: a comparison of oxaprozin and ibuprofen. Semin Arthritis Rheum 1986;15(3 suppl 2):59-65.

(5) Kolodny AL, Klipper AR, Harris BK, Howard FM, Kahn CB, Riskin WG, Weaver AL, and Willkens RF. The efficacy and safety of single daily doses of oxaprozin in the treatment of osteoarthritis: a comparison with aspirin. Semin Arthritis Rheum 1986;15(3 suppl 2):72-79.

(6) Powell WR, Miller JL, and Sheldon WB. Once-daily oxaprozin and piroxicam compared in osteoarthritis. Semin Arthritis Rheum 1986;15(3 suppl 2):80-85.

(7) Weaver A, Rubin B, Caldwell J, McMahon FG, Lee D, Makarowski W, Offenberg H, Sack M, Sikes D, Trapp R, Rush S, Kuss M, Ganju J, and Bocanegra TS. Comparison of the efficacy and safety of oxaprozin and nabumetone in the treatment of patients with osteoarthritis of the knee. Clin Ther 1995;17(4):735-745.

(8) Makarowski W, Weaver A, Rubin B, Caldwell J, McMahon FG, Noveck RJ, Lee D, Offenberg H, Sack M, Sikes D, Trapp R, Rush S, Kuss M, Ganju J, Bocanegra TS, and Ratliff JM. The efficacy, tolerability, and safety of 1200 mg/d of oxaprozin and 1500 mg/d of nabumetone in the treatment of patients with osteoarthritis of the knee. Clin Ther 1996;18(1):114-124.

HFD 550/ Yaciw

JUN 26 1997

MEDICAL OFFICER REVIEW

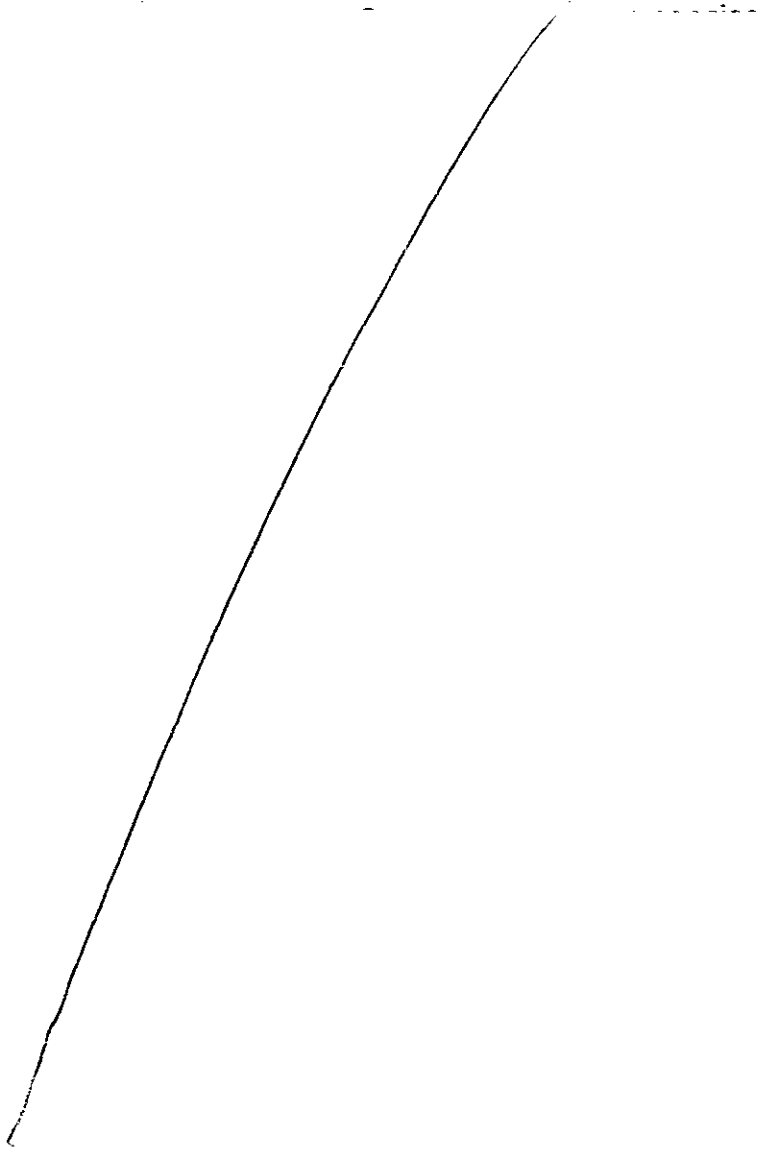
NDA Number:	18-841 Labeling supplement & Phase 4 studies
Date Received (letter date):	June 14 and December 10, 1996
Date Assigned for Review:	December 16, 1996
Dates Reviewed:	December 16 to 20, 1996
Sponsor:	G.D.Searle & Co.
Drug Name:	Oxaprozin [DAYPRO®]
Drug Class:	NSAID
Intended Use of Drug:	Therapy of osteoarthritis & rheumatoid arthritis
Consumer Safety Officer:	Chin Koerner
Medical Officer:	Rudolph M. Widmark, M.D., Ph.D.

Background

DAYPRO (oxaprozin) is an approved NSAID which is indicated for acute and long-term use in the management of the signs and symptoms of osteoarthritis and rheumatoid arthritis. The labeled dosage is 600 to 1200 mg per day given in a single dose (q.d.) because of the drug's long half-life (25 to 50 hours). At the time of approval, the Sponsor took the obligation to perform several Phase 4 studies, whose results are in this submission as support of the labeling changes for DAYPRO (oxaprozin).

Proposed Labeling Changes and the Data Supporting Them

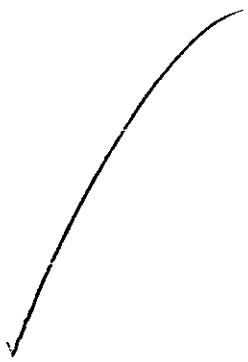
Below are the labeling changes proposed by the Sponsor (in *italics*) followed by the Reviewer's comments and conclusions:

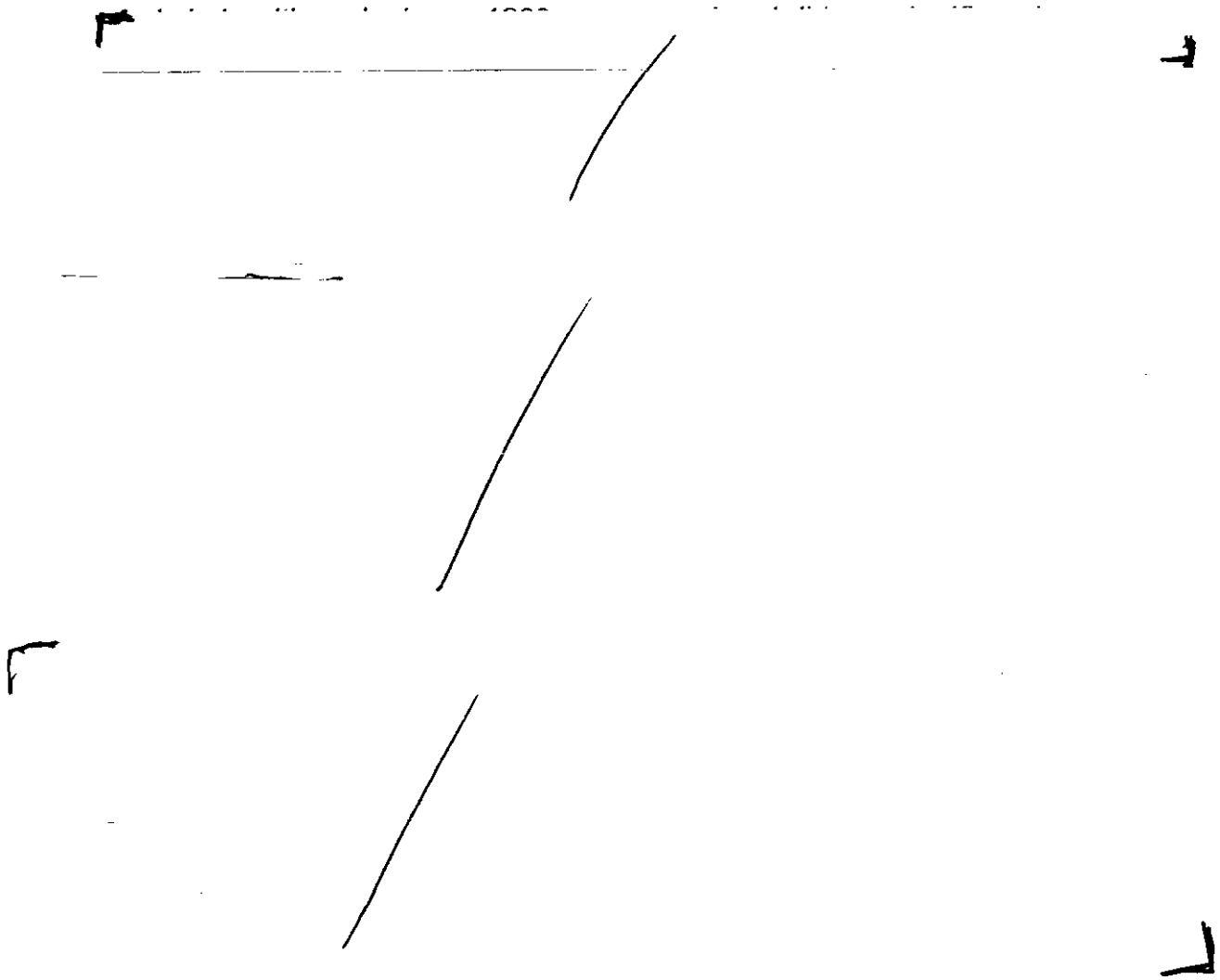


All of the above mentioned changes are based on the results of a study conducted by the Sponsor and entitled "The Effects of DAYPRO® (Oxaprozin) 1200 mg QD on Platelet Function in Normal Healthy Subjects." In this open-label trial, 15 healthy male subjects (7 whites and 8 blacks) received 1200 mg DAYPRO daily for 8 days. Six untreated male subjects were used as 'placebo'-controls. Platelet aggregation tests and template bleeding time were performed 4 and 24 hours after DAYPRO-dosing on Day 1 and Day 8. All subjects had to return to the in-

vestigator on Day 12 for ADR assessment, template bleeding time and platelet aggregation tests. Subjects with a bleeding time >7 minutes and/or platelet aggregation decrease by >50% were to have these tests repeated on Day 15 and, if needed, on Day 21. Of the 15 subjects in the DAYPRO group, only 11 completed the study (2 were lost to follow-up and 2 had pre-existing conditions that disqualified them to participate in the trial). Of the 6 subjects in the placebo group, 5 completed the study (1 was lost to follow-up). Thus, we have DAYPRO data from 11 subjects to be compared to 'no-treatment' data from 5 subjects.

The template bleeding time is a pretty stable laboratory parameter in the same individual over a reasonably short period of time (2 weeks) if nothing intervenes that could possibly influence it. In this trial, the only factor that could influence it would be the ingestion of oxaprozin. From the graph, that depicts the mean template bleeding times for the two treatment groups (oxaprozin and 'placebo') [vol. 65.15, page 56 of 59], it is obvious that only the DAYPRO-treated subjects had a prolongation of the bleeding time. When looked at individually, none of the 'placebo' subjects had any prolongation of the bleeding time, whereas 3 out of the 11 individuals on oxaprozin had no prolongation as compared to baseline; a 20% to 50% post-dosing prolongation was found in 6 subjects, and two had a prolongation of their bleeding time of 100% and above (subjects 1 and 5). The lack of statistical significance of the mean values between active drug and no-drug are meaningless because of the small sample size: if one considers that two, otherwise healthy, subjects in this study had a significant prolongation of the bleeding time after taking DAYPRO, because of the sample size of 11 test subjects, the 95% probability is that about 50% of all patients treated with DAYPRO may have a significant prolongation of their bleeding time. Another shortcoming of this study is the fact that it did not include women, who make up 70 to 80% of the patient population in which DAYPRO will be used. The next time the Sponsor plans to conduct a similar study, it should be placebo-controlled and double-blinded, and include a few subjects treated with a known active control drug, such as aspirin. For the above reasons, the conclusions of





Conclusions

The conclusions of this review are the underlined parts of the main section **Proposed Labeling Changes and the Data Supporting Them.**

Dm. Widmark 12-20-96

Rudolph M. Widmark, MO Date

JEH 1-14-97

Div Director's Comments
See also Class Labeling Guidance
6/24/97

cc: Orig. NDA 18-841
HFD-550
HFD-340
HFD-550/CSO/CKoerner
HFD-550/MChang
HFD-550/CHEM/CYaciw
HFD-550/PHARM/CChen
HFD-550/MO/RWidmark
HFD-550/SMO/JHyde
HFD-550/DIR/WChambers