CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-776

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

HFD 550/Orig.

MAY 6 1998

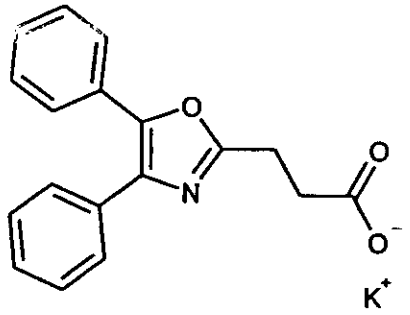
Clinical Pharmacology/Biopharmaceutics Review

Oxaprozin potassium 600 mg Tablets	G. D. Searle & Co.
	Skokie. IL 60077
Reviewer: A. Noory	Submission Date:
NDA 20-776	May 19,1997; Dec. 8, 1997

Review of an NDA

I. Background:

(oxaprozin potassium) is a member of the propionic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). is a salt form of Daypro® (NDA 18-841) which has been marketed by the sponsor since 1992 for the management of the symptoms of osteoarthritis and rheumatoid arthritis. Because Daypro® has a delayed absorption profile, Searle has developed this potassium salt of oxaprozin which has increased solubility to the acid form (370mg/ml versus <10mg/ml). This improvement in the solubility should result in a faster onset of therapeutic effect. The sponsor is seeking approval for the relief of the symptoms of osteoarthritis and rheumatoid arthritis. The chemical name of is 4, 5-diphenyl-2-oxazolepropionic acid, potassium salt. The empirical formula for oxaprozin potassium is $C_{18}H_{14}NOK$, with a molecular weight of 331. It is a white to off-white powder and is freely soluble in water and slightly soluble in alcohol. Oxaprozin potassium has the following structure:



II. Recommendation:

In support of the pharmacokinetic and bioavailability portion of this NDA the sponsor has submitted the results of five pharmacokinetic studies. Pharmacokinetics of oxaprozin potassium upon multiple dose administration has been defined, and the effect of food on the bioavailability of nas been determined. Additionally, the sponsor demonstrated the bioequivalency of the to-be-marketed product manufactured in to the clinical trial formulation manufactured in It is noteworthy to indicate for cross reference that under the NDA 18-841, Daypro®, the sponsor has evaluated the pharmacokinetics of oxaprozin in special patient populations including congestive heart

failure, renal insuficiency, and hepatic disorder. Also under NDA 18-841, the sponsor has undertaken various drug interaction studies. From the Clinical Pharmacology and Biopharmaceutics point of view the NDA 20-776 is approvable.

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III. Overview of pharmacokinetic section:

The human pharmacokinetic and bioavailability section of this NDA consists of five pkarmacokinetic/bioavailability studies:

1. A dose proportionality study of single oral dose of oxaprozin potassium (N48-95-02-008).
2. A multiple dose pharmacokinetic study (N48-95-02-005).
3. A food effect study on bioavailability of oxaprozin potassium (N48-96-02-013).
4. A bioequivalence study of oxaprozin potassium tablets manufactured at two sites (N48-96-02-012) along with in vitro dissolution profiles.
5. A comparative single dose pharmacokinetic study of Daypro® and two oxaprozin potassium salt ratios (N48-94-02-001). (This single dose study does not provide any additional regulatory information that is not contained in the above studies. Therefore this study will not be reviewed)

Formulation:

The composition of — tablet is shown in the following table:

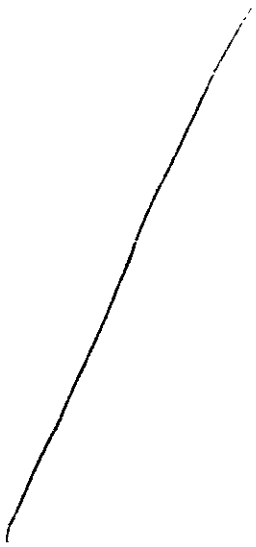
Formulation of to-be-marketed oxaprozin Potassium — Tablets	
Core	mg/tablet
Oxaprozin potassium	—
Microcrystalline cellulose NF	/
Pregelatinized corn starch NF	
Stearic Acid NF	/
Colloidal Silicon dioxide NF	
—	
	/

(Film Coat)	
Blue	
Total Weight of the Tablet	

* - Equivalent to 600 mg of oxaprozin.

Analytical:

The analysis of oxaprozin in human plasma (Method was based on a method published by S.L.McHugh et. al. in the Journal of Pharmaceutical Science, 69, (7), 794 (1980) with some modification. The analysis was done by High Performance Liquid Chromatography (HPLC) using a with UV detection The human plasma was extracted using diethyl ether under acidic conditions. Ketoprofen was used as the Internal Standard. The assay was shown to be specific for oxaprozin and linear over a range of The assay had a limit of detection of , which corresponds to an oxaprozin plasma concentration of µg/ml. The analysis of unbound oxaprozin in human plasma (Method was also done by High Performance Liquid Chromatography (HPLC) using a with UV detection at The assay was specific for oxaprozin and linear over the range of The assay was shown to be specific for oxaprozin. The assay had a limit of detection of which corresponds to an oxaprozin plasma concentration of A summary of the assay for each study is included in the appendix. A representative sample chromatogram is shown below.



A. Dose Proportionality Study:

Thirty six (36) healthy subjects (18 males and 18 females; age 21 - 78 years) were enrolled in this single dose, randomized three way crossover study and all subjects completed the study. Subjects were placed in three groups, young, middle-aged, and elderly. Each group consisted of six males and six females. A summary of the study and data are located on pages 13 - 19 of the appendix and a summary of the result is presented in the following tables.

AUC $_{(0-\infty)}$: Single Doses of Oxaprozin Potassium; Mean ± SD, N=36					
Total Oxaprozin (μg*h/ml)			Unbound Oxaprozin (ng*h/ml)		
600 mg	1200 mg	1800 mg	600 mg	1200 mg	1800 mg
5817.5±1582.9	9622.7±2322.6	12609.3±3269.5	5076.9±1732.7	11310.2±3735.7	19291.4±6439.8

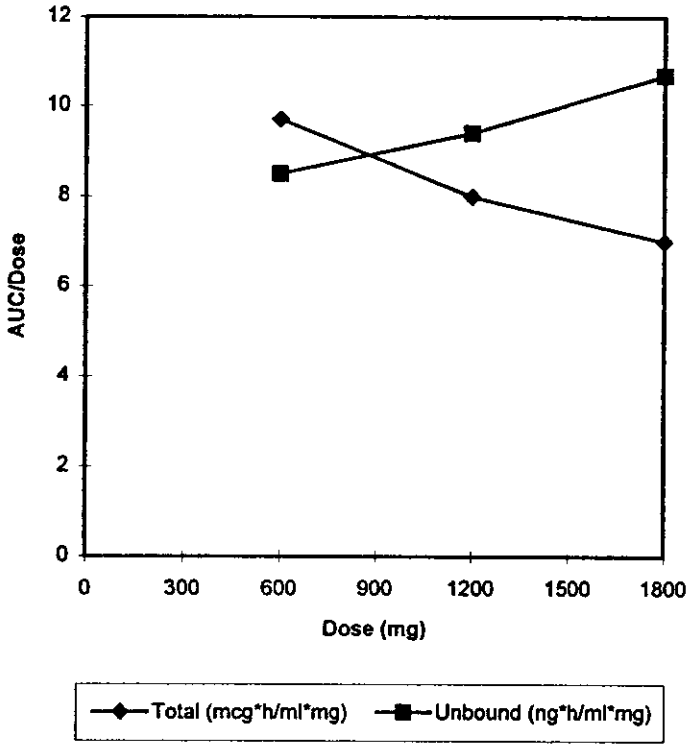
To present the trend independent of the dose, the values presented in tables below are adjusted for dose i.e. the pk-parameter divided by dose.

Dose Proportionality of Single Doses of Oxaprozin Potassium; Mean ± SD, N=36								
	Total Oxaprozin (μg*h/ml*mg)				Unbound Oxaprozin (ng*h/ml*mg)			
PK-parameter	600 mg	1200 mg	1800 mg	P-value	600 mg	1200 mg	1800 mg	P-value
$AUC_{(0-\infty)}$	9.7 ±2.6	8.0 ± 1.9	7.0 ± 1.8	0.0001*	8.5 ± 2.9	9.4 ± 3.1	10.7 ± 3.6	0.0001*

* - Statistically Significant at 0.05 level

The data from this single dose study show that there is a lack of dose proportionality for both total and unbound oxaprozin (p-value <0.05). While the AUC for total oxaprozin decreases with an increase in dose from 600mg to 1800mg over a dose normalized baseline, the AUC for the unbound oxaprozin increases as shown in the following figure. This lack of proportionality between the dose and the AUC is due to the nonlinear protein binding characteristic of oxaprozin.

Dose Proportinality of ~ in All Subjects



The two tables below also contain the dose adjusted PK-parameters (parameter/dose) of AUC and C_{max}, for subgroups of males and females.

Dose Adjusted** Pharmacokinetic Parameters of Total Oxaprozin; mean ± SD ; N=6										
		600 mg			1200 mg			1800 mg		
PK param	Group	Male	Female	% Diff	Male	Female	% Diff	Male	Female	% Diff
AUC(0-∞) µg*hr/mg*ml	young	9.2±3.18	10.7±3.24	+16	7.6±2.07	8.9±2.48	+17	6.8±2.21	7.7±2.03	+13
	Middle-aged	9.2±0.88	8.8±2.35	-4	7.4±1.04	7.4±1.55	0	6.5±0.64	6.4±1.05	-2
	Elderly	8.5±2.47	11.8±2.43	+39	7.3±1.89	9.6±1.80	+32	6.1±1.92	8.4±2.03	+38
Cmax µg/mg*ml	young	0.14±0.025	0.16±0.012	+14	0.12±0.019	0.14±0.002	+17	0.11±0.008	0.12±0.11	+9
	Middle-aged	0.13±0.019	0.14±0.019	+8	0.12±0.010	0.14±0.19	+17	0.10±0.013	0.12±0.011	+20
	Elderly	0.13±0.013	0.18±0.015	+38	0.11±0.01	0.14±0.018	+27	0.11±0.015	0.13±0.014	+18

**- Dose adjusted = parameter/dose.

Dose Adjusted** Pharmacokinetic Parameters of Unbound Oxaprozin; mean ± SD ; N=6										
		600 mg			1200 mg			1800 mg		
PK param	Group	Male	Female	% Diff	Male	Female	% Diff	Male	Female	% Diff
AUC(0-∞) ng*hr/mg*ml	young	7.5±3.47	9.1±3.44	+21	8.6±3.69	10.3±2.99	+20	9.3±4.20	11.8±3.50	+27
	Middle-aged	7.6±0.66	8.6±3.33	+13	8.0±1.06	9.6±3.18	+20	9.4±0.40	10.6±3.21	+13
	Elderly	7.0±1.89	10.9±2.67	+55	7.3±1.81	12.9±2.59	+77	8.5±2.45	14.7±3.52	+73
Cmax ng/mg*ml	young	0.18±0.045	0.21±0.025	+17	0.24±0.082	0.36±0.088	+50	0.34±0.097	0.46±0.159	+35
	Middle-aged	0.17±0.035	0.21±0.052	+24	0.24±0.031	0.39±0.118	+63	0.35±0.074	0.48±0.148	+37
	Elderly	0.16±0.015	0.30±0.057	+88	0.22±0.044	0.50±0.152	+127	0.37±0.057	0.63±0.188	+70

**- Dose adjusted = parameter/dose.

The results indicate that the exposure to the total oxaprozin in the elderly females is about 38% greater than the elderly males, and the exposure to the unbound oxaprozin in the elderly females is about 73% greater than the elderly males. This increased exposure seen in the elderly female population is most likely due to two factors. One is the nonlinear protein binding characteristic of oxaprozin where small changes in concentration is magnified in the elderly, and second the difference in the body weight. If we multiply the mean dose adjusted AUC by their respective mean weight and compare the results, we notice that the difference will reduce from 38% to 11% for the total oxaprozin and for the unbound oxaprozin the difference will reduce from 73% to 39% respectively.

B. Multiple dose pharmacokinetic study:

Forty healthy volunteers (26 males and 14 females; age range of 18 to 40) were enrolled in this multiple dose randomized parallel study and thirty six subjects completed the study. Subjects were placed in three treatment groups (12 subject in each group). The treatments were Daypro® (oxaprozin acid) — and 100% oxaprozin potassium. In this review, only the pharmacokinetics of Daypro® and the 100% potassium salt will be considered as the sponsor is seeking approval for this product only. Pages 20 - 26 of the appendix contain the summary of this study.

The table below contains the mean ± SD of pharmacokinetic parameters and the 90% confidence interval of the log-transformed data for total oxaprozin.

PK- Parameters for Total Oxaprozin After Multiple Doses of (1200 mg QD); Mean ± SD; N=12				
PK-parameter	—	Daypro®	Ratio (T/R)	90% Confidence Interval
AUC (0-24) (μg*h/ml)	4246.0 ± 644.2	4213.0 ± 1423.9	1.01	92.8 - 117.0
C_{max} (μg/ml)	258.73 ± 32.51	238.84 ± 54.08	1.08	100.9 - 119.4
C_{min} (μg/ml)	131.61 ± 18.88	134.33 ± 56.08	0.98	90.3 - 118.5
C_{SS} (μg/ml)	176.92 ± 26.84	175.54 ± 59.33	1.01	
T_{max} (hr)	2.12 ± 1.36	2.44 ± 0.69	0.87	
$T_{1/2}$ (hr)	38.04 ± 11.11	39.34 ± 7.92	0.97	
$(C_{max} - C_{min})/C_{min}$	0.98 ± 0.15	0.89 ± 0.35	1.10	
R	1.63	1.79	0.91	
$T_{1/2}$ (Acc) (hr)	17.5	20.3	0.86	

The results indicate that — behaves similar to Daypro® with respect to AUC, Cmax, and Cmin, the 90% confidence intervals are within the 80 - 125, limits for bioequivalence. Also it is notable that the median Tmax on day eight is 25% less for — than for Daypro®, 1.5 hours versus 2 hours respectively (page 21 of the appendix).

C. Food effect study:

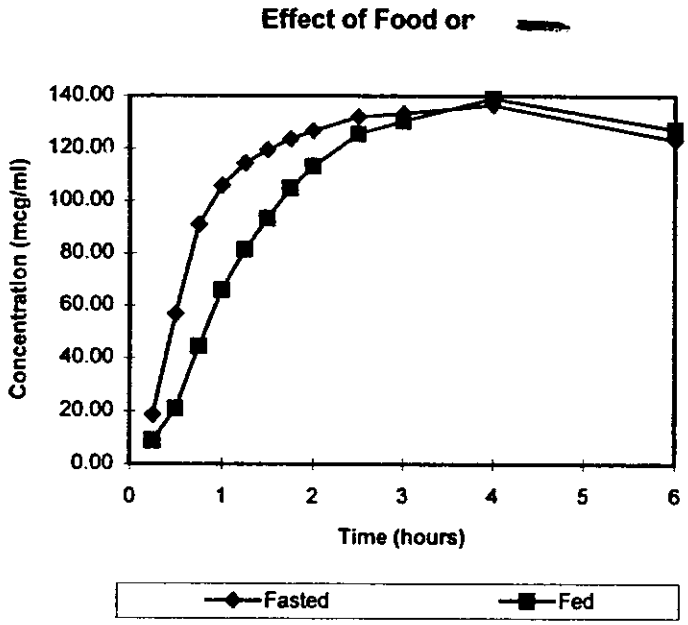
The effect of food on — was assessed in protocol number N48-96-02-013. Forty eight (48) volunteers (36 males; 12 females) participated in this single dose, randomized, parallel design study. Twenty four (24) subjects were assigned to each treatment arm and all subjects completed the study. The most common adverse event experienced by the subjects was headache (13% in the fasting state; 17% in the fed state) and abdominal pain (13% in the fasting state). Both events were of mild to moderate severity. Subjects received two tablets of to-be-marketed oxaprozin potassium — equivalent to 1200mg of oxaprozin acid, after an overnight fast or postprandial. Blood samples were collected for

determination of total and unbound oxaprozin concentration for up to 240 hours post drug administration. The food used in this study consisted of one slice bread with butter, two ounces of hash brown, two fried eggs, two slices of bacon, and eight ounces of whole milk. This meal contains less fat and calories from that of the FDA's high fat meal. It used half the recommended amount of bread and hash brown i.e. one slice of bread instead of two, and two ounces of hash brown instead of four ounces. Upon consultation with Dr. Ameeta Parekh, the Agency's expert on food effect studies, it was learned that the food used in this study falls a bit short of the recommended fat and calorie content. Since the 90%CI is not on border line, the fat and calorie content of the meal is sufficient at this time. Pages 27 - 30 of the appendix contain the result of this study and a summary of the result is shown in the following two tables:

Effect of Food on the Total Oxaprozin; Mean ± SD (%CV)				
Pk-Parameter	Fed	Fasted	Ratio (Fed/Fasted)	90% C.I.
AUC $_{(0-\infty)}$ (µg*h/ml)	9647 ± 2385 (25)	9994 ± 2145 (22)	0.96	86 - 107
C_{max} (µg/ml)	146.0 ± 20.8 (14)	147.3 ± 19.9 (14)	0.99	93 - 106
T_{max} (hr)	3.67 ± 1.51 (41)	2.69 ± 1.11 (41)	1.36	113 - 160

Effect of Food on the Unbound Oxaprozin; Mean ± SD (%CV)				
Pk-Parameter	Fed	Fasted	Ratio (Fed/Fasted)	90% C.I.
AUC $_{(0-\infty)}$ (µg*h/ml)	9948 ± 3068 (31)	10477 ± 3362 (32)	0.95	83 - 109
C_{max} (µg/ml)	273.9 ± 92.1 (34)	278.8 ± 91.7 (33)	0.98	84 - 115
T_{max} (hr)	3.55 ± 1.62 (46)	2.76 ± 1.31 (48)	1.29	103 - 154

A log transformed ANOVA showed no significant difference with respect to AUC or C_{max} between treatments. The 90% confidence intervals of the ratio (fed:fasted) for both AUC and C_{max} were within the 80 to 125%. Although there is no food effect on the AUC or C_{max}, the time to reach the maximum concentration (T_{max}) is significantly longer for the fed state than the fasted. The figure below represents this phenomenon (N=24).



Based on the results of this food effect study, it is recommended that be administered in the fasting state when acute analgesia is desired.

D. Bioequivalence:

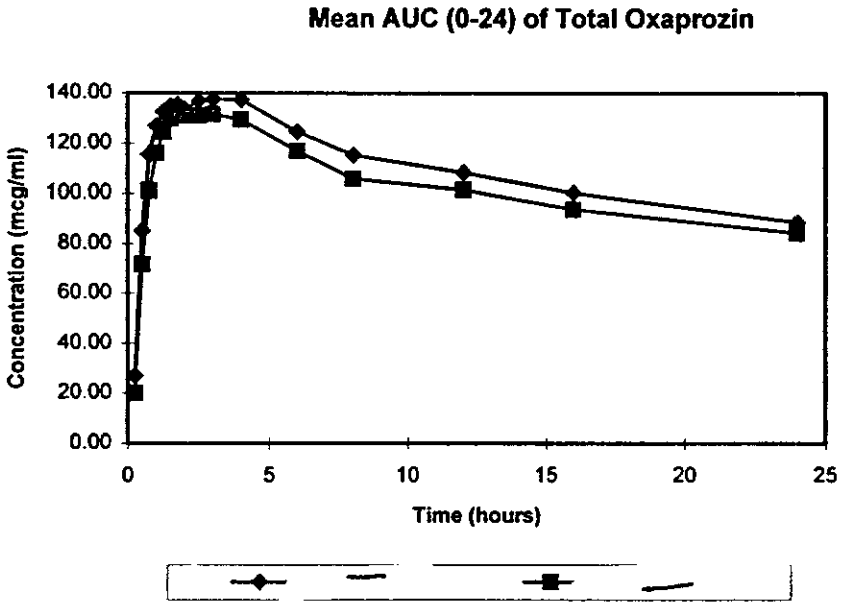
The maufacturing of oxaprozin potassium for the clinical trial was done in the . The sponsor is planing to register the to- be-marketed formulation that was manufactured at the production facility in This study was conducted to demonstrate that these two products are bioequivalent with respect to AUC and C_{max}.

A detailed study summary data is located on pages 31 - 34 of the appendix and a summary result is shown in the two tables below. Analysis of variance (ANOVA) on the weight corrected and log-transformed AUC and C_{max} showed no significant difference for the total and the unbound oxaprozin between the two products. A least square mean and the 90% confidence interval of the ratios for both AUC and C_{max} were within the 80% - 125% for total and unbound oxaprozin.

Comparison of the To-be marketed formulation to the formulation used in the Pilot Clinical trial; Total Oxaprozin				
PK-Parameter	Test	Reference	Test/Reference	90% Confidence interval
$AUC_{(0-\infty)}$ (µg*h/ml)	9056.9	9488.9	0.95	84.7 - 106.2
C_{max} (µg/ml)	153.81	143.65	1.07	99.4 - 114.7

Comparison of the To-be marketed formulation to the formulation used in the Pilot Clinical trial; Unbound Oxaprozin				
PK-Parameter	Test	Reference	Test/Reference	90% Confidence interval
$AUC_{(0-\infty)}$ (ng*h/ml)	9169.6	9773.6	0.94	81.1 - 106.5
C_{max} (ng/ml)	311.35	313.13	0.99	81.6 - 117.3

The findings of this study indicates that the oxaprozin tablets manufactured in — are bioequivalent to the oxaprozin tablets manufactured in — The figure below shows the AUC for the initial 24 hours.



E. Dissolution:

The sponsor has carried out a comparative in vitro dissolution on the to-be-marketed batch as well as the batch used in the pilot clinical trial. The dissolution methodology used for — is the same as the established dissolution method for Daypro®. The result of the dissolution test are located in page 34 of the appendix. The dissolution methodology and specification proposed by the sponsor is:

Apparatus:	USP apparatus II (paddle)
Paddle speed:	75 RPM
Dissolution medium:	Phosphate buffer (0.05 M), pH 7.4
Dissolution volume:	1000 ml at 37 ^{O}C
Dissolution Specification:	Q=75% at 45 minutes

The summary result of the dissolution test for the to-be-marketed product is shown in the following table and graph:

In Vitro Dissolution of Oxaprozin Potassium Tablets (Lot # PT-106-95); Mean (%RSD); N=12						
Time	10 Min	15 Min	20 Min	30 Min	45 Min	60 Min
% Dissolved	67 (12)	88 (6)	97 (2)	99 (1)	99 (1)	99 (1)

Dissolution of Oxaprozin Potassium Tablets

Time (minutes)

A dissolution methodology with paddle speed of 75 RPM is a bit too fast for the highly soluble oxaprozin potassium salt. Additionally, the current USP's recommendation for simulated intestinal fluid (SIF) is pH 6.8 (USP 23 Supplement 7 page 4082). If the sponsor wishes to use the same dissolution methodology as used for Daypro®, this is acceptable. However, the proposed dissolution specification is not appropriate for — as the solubility of the potassium salt of oxaprozin is about forty times more than the solubility of the oxaprozin acid. Therefore, it is necessary to establish a dissolution specification capable of batch to batch discrimination. Based on the dissolution data of both the to-be-marketed batch and the batch used in the pilot clinical trial a dissolution specification of not less than (NLT — in 20 minutes is recommended for — The interim dissolution methodology and specification for the quality control of — should be:

Apparatus:	USP Apparatus II (paddle)
Paddle speed:	75 RPM
Dissolution medium:	Phosphate buffer (0.05 M), pH 7.4
Dissolution volume:	1000 ml at 37 °C
Dissolution Specification:	Q= — in 20 minutes

IV. Labeling Recommendation:

The following changes are recommended for the pharmacokinetics portion of the labeling

Absorption

Distribution:

Metabolism:
(replace the paragraph with the following)
Oxaprozin's metabolites are considered not to be pharmacologicaly active and they have been found in both human urine and feces. Oxaprozin is primarily metabolized by the liver, by both microsomal oxidation (65%) and glucuronic acid conjugation (35%). Ester and ether glucuronides are the major conjugated metabolites of oxaprozin. A small amount (<5%) of active phenolic metabolites are produced, but the contribution to overall activity is limited.

Excretion:
(replace the paragraph with the following)
Sixty-five percent (65%) of the dose is excreted into the urine and 35% in the feces as metabolite. Even though renal elimination is a significant pathway of elimination, dosing adjustment in patients with mild to moderate renal dysfunction is not necessary. Biliary excretion of unchanged oxaprozin is a minor pathway. The accumulation half life of oxaprozin in healthy subjects is approximately 18 hours and the elimination half life is about 38 hours.

V. Comments to be sent to the sponsor:

It is recommended that a new dissolution methodology be developed based on the current USP recommendation for [redacted]. We request that the sponsor would submit the results of this dissolution test within six months.

It is recommended that for future food effect studies the sponsor uses the recommended "FDA high fat breakfast" which consists of two slices of toasted white bread with butter, two eggs fried in butter, two slices of bacon, four ounces of hash brown potatoes and eight ounces of whole milk.

A Noory 5/6/98

Assadollah Noory
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm.D. EDB 5/6/98
CC: NDA 20-776 (ORIG),
HFD-550/DIV. File
HFD-550/CSO/Lutwak
HFD-880 (Noory)
HFD-880 (Bashaw)
HFD-880 (Lazor)
(CDR. Attn: Barbara. Murphy)
HFD-344 (Viswanathan)

Appendix

NDA # 20-776 Submission Date: May 19,1997 Volume: 1.9 & 1.10
Study Type: Dose Proportionality Study # N N48-95-02-008
Study Title: Dose Proportionality Of Single Oral Doses Of Oxaprozin potassium

Clinical Investigator: [redacted] Analytical Investigator: [redacted]
Site: Site: [redacted]

Study Objective: 1. To determine if the plasma concentration of total and unbound oxaprozin are proportional to to the single oral doses of 600mg, 1200mg, and 1800mg of oxaprozin salt.
2. To determine if the plasma concentration of total and unbound oxaprozin are proportional to to the single oral doses of 600mg, 1200mg, and 1800mg of oxaprozin salt in six subgroups of the subject population: young, middle-aged, and elderly males; and young, middle-aged, and elderly females.

Study Design:

Single Dose: X	Multiple Dose:	Randomized: X	Washout Period: Three weeks
Cross-Over: X	Parallel:	Other Design:	Single Center: X
Fasted: X	Post Dosing:		
Food Study:	Food Type:		

Study Subjects: Thirty six healthy subjects (18 males and 18 females; age 20 - 86 years) were enrolled in this study and all subjects completed the study. Subjects were placed in three groups (young, middle-aged and elderly

Subject Breakdown

GROUP	AGE GROUP.	MALE / FEMALE #
Young	18 -45	6 / 6
Middle-aged	46 - 65	6 / 6
Elderly	>65	6 / 6

Drug Products

Drug product	Dose	Dosage form	Strength	Packing lot #	Batch #
Oxaprozin potassium	600,1200,1800 mg QD	Caplets	600 mg	RCT 9942	PT-063-95

Sampling Times

Plasma: Blood samples were collected at pre-dose, and at 0.25, 0.5,0.45, 1, 1.25, 1.5, 1.45, 2, 2.5, 3, 4, 6, 8,12, 16, 24, 36, 48, 72, 96, 144, 192, and 240 hours after dose administration.

Assay Method: HPLC with UV detection was used for determination of oxaprozin (total oxaprozin at [redacted] unbound oxaprozin at [redacted].

Assay Sensitivity: For total oxaprozin [redacted] for unbound oxaprozin: [redacted]

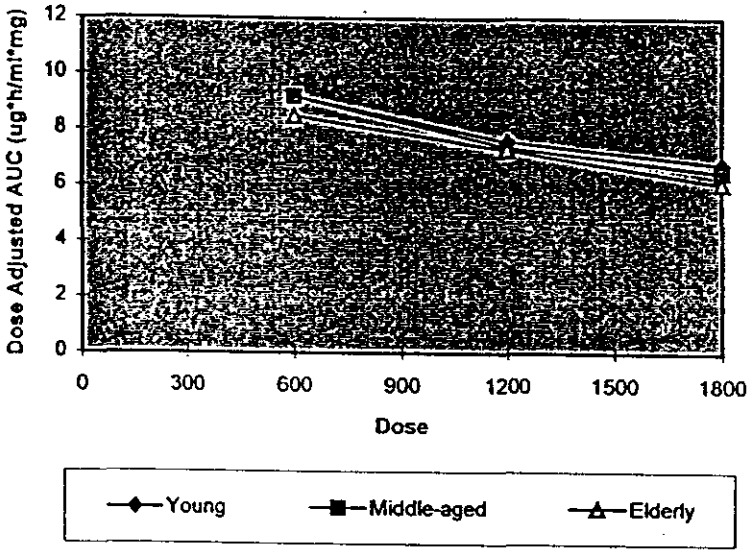
Assay Accuracy: %RE range for total oxaprozin from [redacted] for unbound oxaprozinv (aqueous QC) from [redacted]

Assay Precision: %RSD range for total oxaprozin from [redacted], for unbound oxaprozin from [redacted]

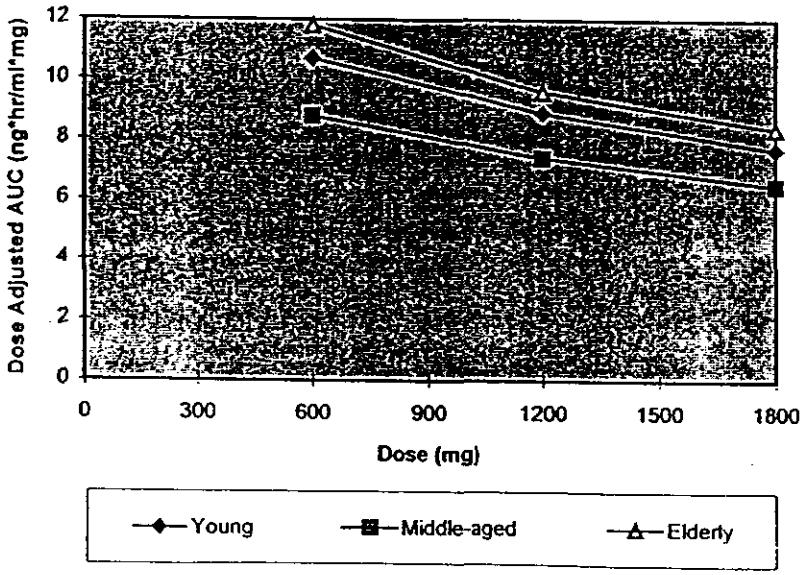
Results:

The data from this single dose study show that there is not a proportional increase in AUC of total or unbound oxaprozin as the dose increases from 600mg to 1800mg. The following graphs demonstrate this phenomenon independent of dose meaning that ideally the trend should be a straight line parallel to the X-axis.

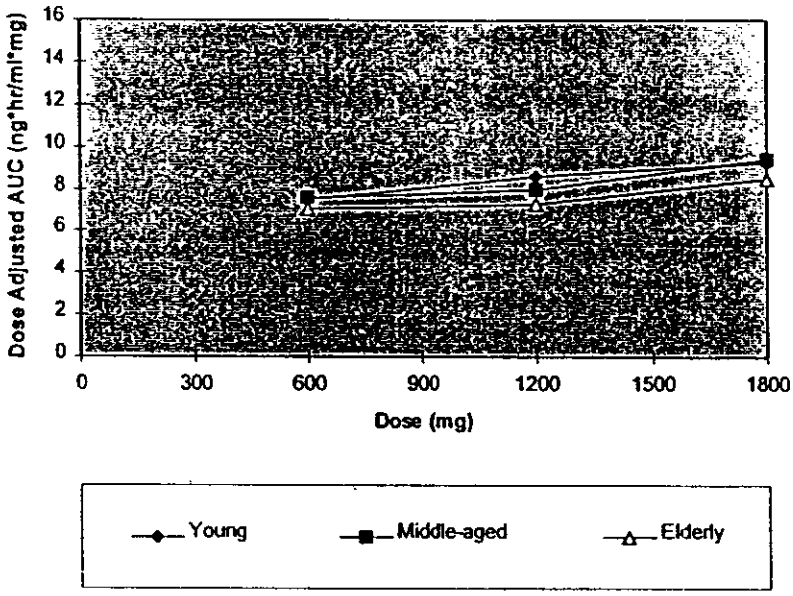
Total Oxaprozin in Males



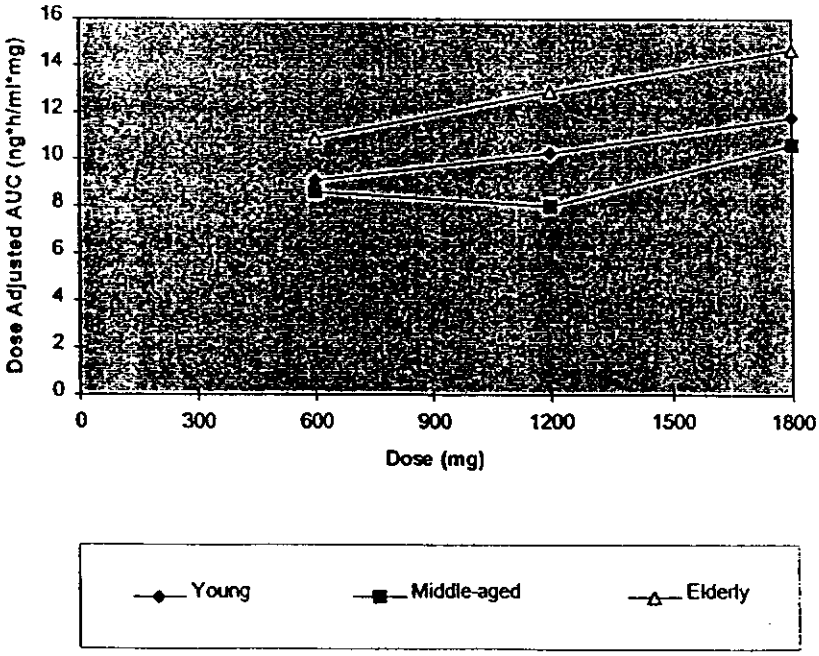
Total Oxaprozin in Females



Unbound Oxaprozin in Males



Unbound Oxaprozin in Females



NDA # 20-776 Submission Date: May 19,1997 Volumes: 1.13 & 1.14
Study Type: Multiple dose pharmacokinetic Study # N48-95-02-005
Study Title: Pharmacokinetic Profile of Multiple Oral Doses of Three Formulations of Oxaprozin (1200mg QD) in Healthy Volunteers

Clinical Investigator: [redacted] Analytical Investigator [redacted]
Site: [redacted] Site: [redacted]

Study Date: 22 May 1995 - 12 june 1995

Study Objective: 1. To compare the pharmacokinetic profiles of oxaprozin of total and unbound oxaprozin for two formulations of oxaprozin potassium, each equivalent to 1200 mg of oxaprozin acid, to Daypro® (oxaprozin acid 1200mg) after single and multiple oral doses.
2. To assess the safety and tolerability of two formulations of the oxaprozin potassium, each equivalent to 1200mg of oxaprozin acid, and compare them to Daypro® given once daily for eight days.

Study Design:
Single Dose: Multiple Dose: X Randomized: X Washout Period:
Cross-Over: Parallel: X Other Design:
Fasted: Post dosing
Food Study: Food Type:
Study Subjects: Forty healthy volunteers (26 males and 14 females; age range of 18 to 40) were enrolled in this study and were placed in three groups according to the following table. Thirty six subjects completed the study (12 subject in each group).

Subject Breakdown

Group #	No. of Subj.	Male/ Female	Mean Age (yr)	Range (yr)	Mean Weight (kg)	Range (kg)
1	13	10 / 3	28.1	19 - 40	74.9	47.2 - 95.8
2	12	4 / 8	26.5	18 - 37	61.3	49.0 - 74.9
3	15	12 / 3	29.4	20 - 40	71.3	60.8 -81.7

Treatments

Group #	Treatments*	Dose	Dosage Form	Strength	Mfg./package Lot #	Batch Size
1	Daypro®	1200 mg QD	Caplets	600 mg	RCT 9828	not provided
2	[redacted]	1200 mg QD	Tablets	600 mg**	TC-094-95	[redacted] tablets
3	100%Salt	1200 mg QD	Tablets	600 mg**	TC-093-94	[redacted] tablets

* - Oxaprozin Acid (Daypro®); 60% [redacted] 100% oxaprozin potassium.
** - Tablets contain oxaprozin that are equivalent to 600 mg oxaprozin acid.

Sampling Times

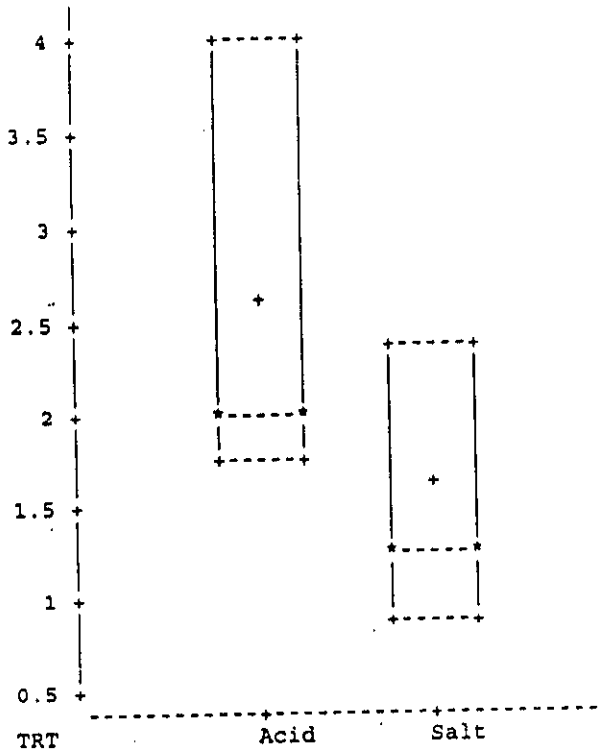
Plasma: Blood samples were collected on days [redacted] [redacted] hours after dose administration. On day 8 additional blood samples were collected at [redacted] after dosing.
Assay Method: [redacted] detection was used for determination of oxaprozin (total oxaprozin at [redacted] unbound oxaprozin at [redacted]
Assay Sensitivity: For total oxaprozin: [redacted] for unbound oxaprozin: [redacted]
Assay Accuracy: %RE range for total from [redacted] for unbound (aqueous QC) from [redacted]
Assay Precision: %RSD range for total from [redacted] for unbound from [redacted]

Study Conclusion:
[redacted] behaves very much like Daypro® with less variability and on the average the time to reach the maximum concentration is shorter for [redacted] than Daypro®.

Day one

Univariate Procedure
Schematic Plots

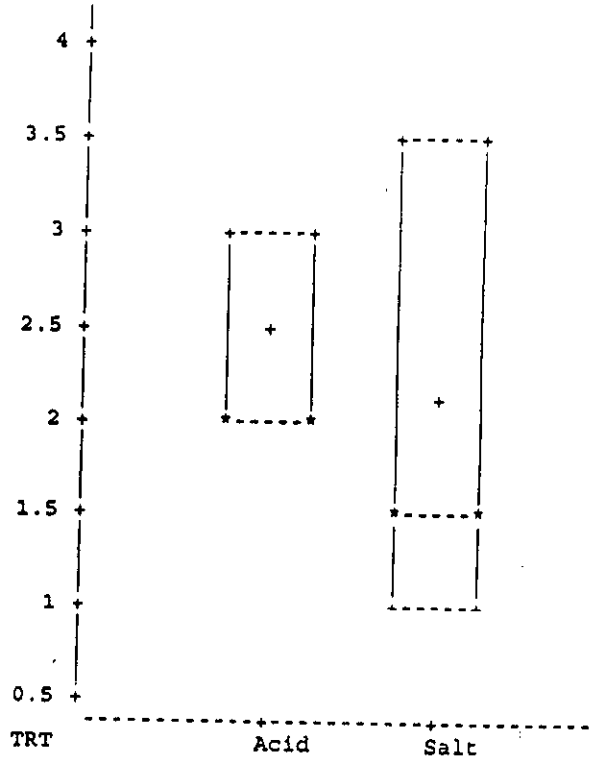
Variable=TMAX



Day Eight

Univariate Procedure
Schematic Plots

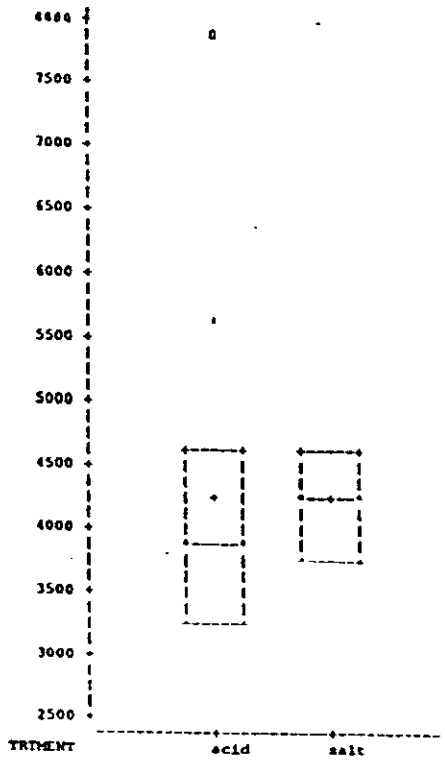
Variable=TMAX



Day 8

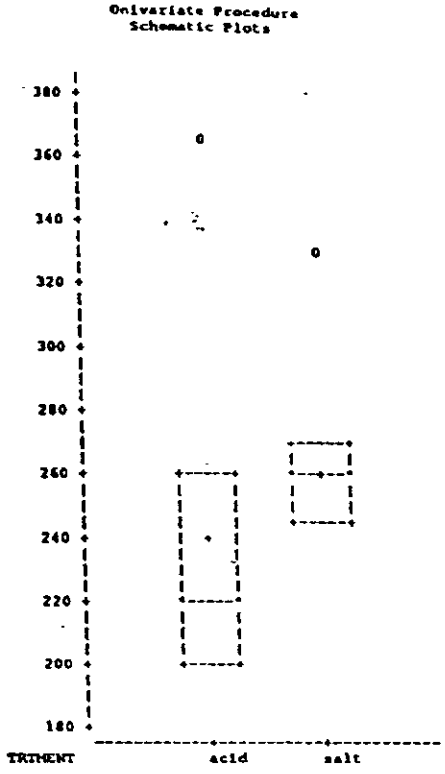
Univariate Procedure
Schematic Plots

Variable=AUC24



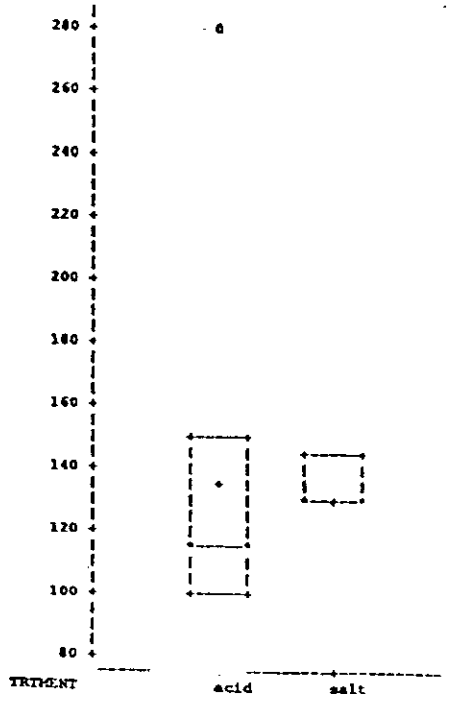
Univariate Procedure
Schematic Plots

Variable=CMAX



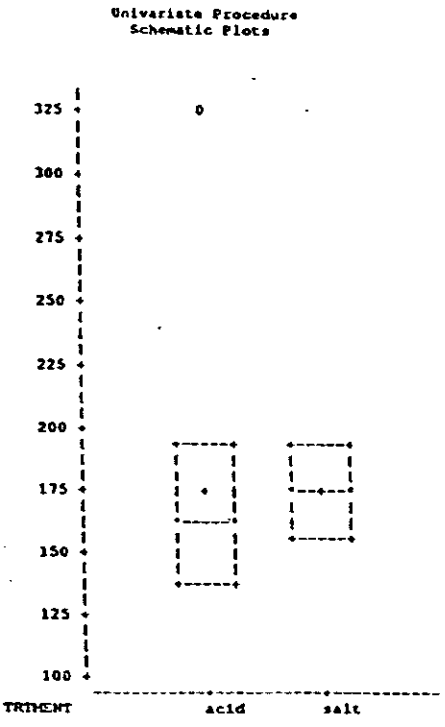
Univariate Procedure
Schematic Plots

Variable=CMIN



Univariate Procedure
Schematic Plots

Variable=CSS



PK PROFILE OF MULTIPLE ORAL DOSES OF OXAPROZIN (1200 MG QD)
W48-95-02-005

TOTAL OXAPROZIN PLASMA CONCENTRATIONS (mcg/ml) (DAY 1)

SUBJECT ID	TREATMENT	AUC (0-24)	CMIN (0-24)	CMAX (0-24)	TMAX (0-24)
002	ACID				
003	ACID				
006	ACID				
010	ACID				
011	ACID				
017	ACID				
022	ACID				
026	ACID				
032	ACID				
033	ACID				
035	ACID				
036	ACID				
00					
00					
012					
016					
018					
019					
021					
028					
029					
034					
040					
041					
001	SALT				
005	SALT				
007	SALT				
008	SALT				
020	SALT				
024	SALT				
025	SALT				
027	SALT				
030	SALT				
031	SALT				
037	SALT				
915	SAL				

NOTE: CMIN = THE PRE-DOSE OXAPROZIN PLASMA CONCENTRATION

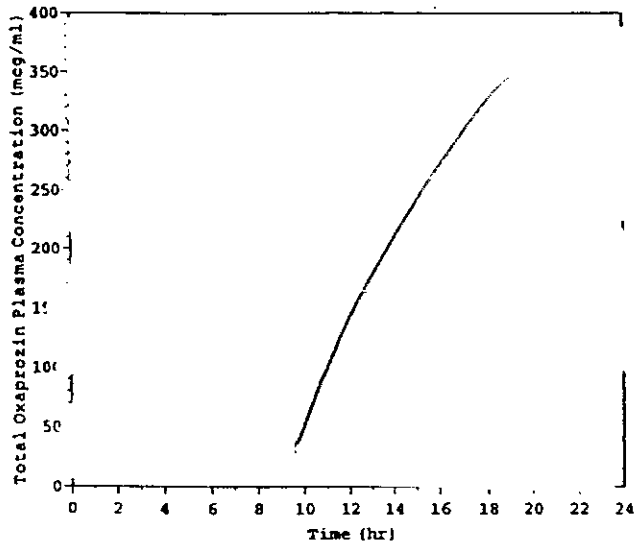
PK PROFILE OF MULTIPLE ORAL DOSES OF OXAPROZIN (1200 MG QD)
W48-95-02-005

TOTAL OXAPROZIN PLASMA CONCENTRATIONS (mcg/ml) (DAY 8)

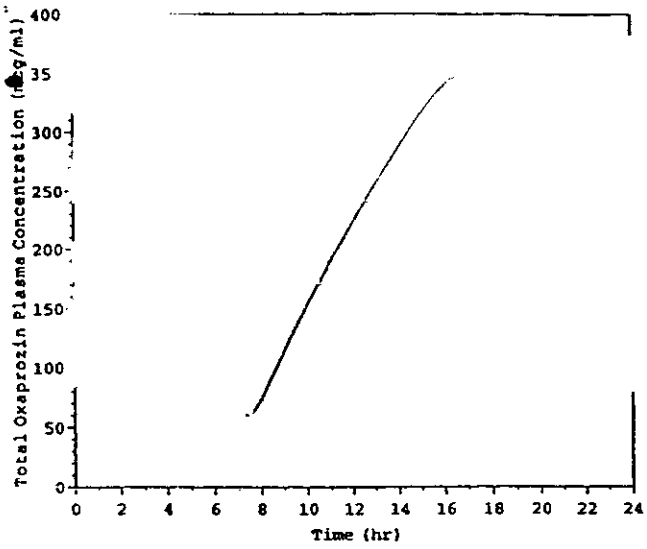
SUBJECT ID	TREATMENT	AUC (0-24)	AUC (0-48)	CMIN (0-48)	CMAX (0-48)	TMAX (0-48)	T1/2 (hr) (0-48)
002	ACID						
003	ACID						
006	ACID						
010	ACID						
011	ACID						
017	ACID						
022	ACID						
026	ACID						
032	ACID						
033	ACID						
035	ACID						
036	ACID						
004							
009							
012							
016							
018							
019							
021							
028							
029							
034							
040							
041							
001	SALT						
005	SALT						
007	SALT						
008	SALT						
020	SALT						
024	SALT						
025	SALT						
027	SALT						
030	SALT						
031	SALT						
037	SALT						
915	SALT						

NOTE: CMIN = THE PRE-DOSE OXAPROZIN PLASMA CONCENTRATION

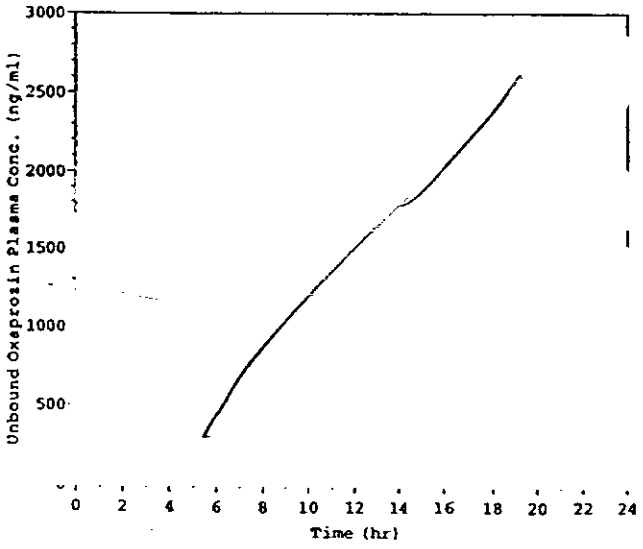
Steady-State Plasma Concentrations of Total Oxaprozin on Day 8 in 12 Healthy Subjects After Multiple Oral Doses of Oxaprozin 1200 mg Once Daily, Administered as [redacted] Oxaprozin Potassium Salt) (data from report no. N48-96-06-005).



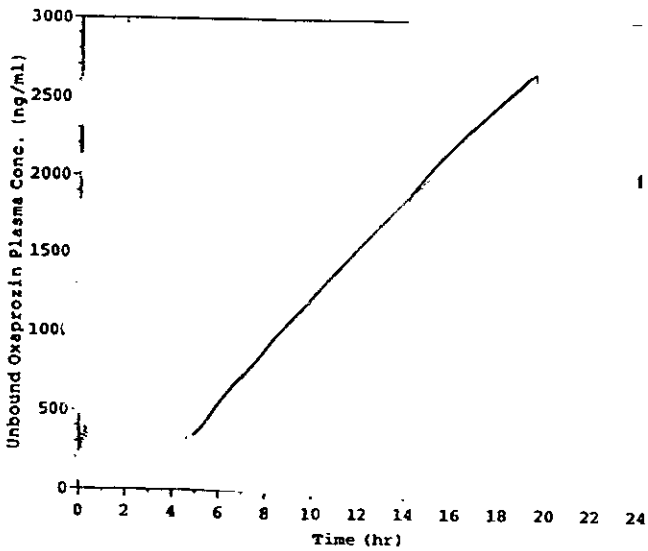
Steady-State Plasma Concentrations of Total Oxaprozin on Day 8 in 12 Healthy Subjects After Multiple Oral Doses of Oxaprozin 1200 mg Once Daily, Administered as Daypro (Oxaprozin Acid) (data from report no. N48-96-06-005).



Steady-State Plasma Concentrations of Unbound Oxaprozin on Day 8 in 12 Healthy Subjects After Multiple Oral Doses of Oxaprozin 1200 mg Once Daily, Administered as [redacted] Oxaprozin Potassium Salt) (data from report no. N48-96-06-005).

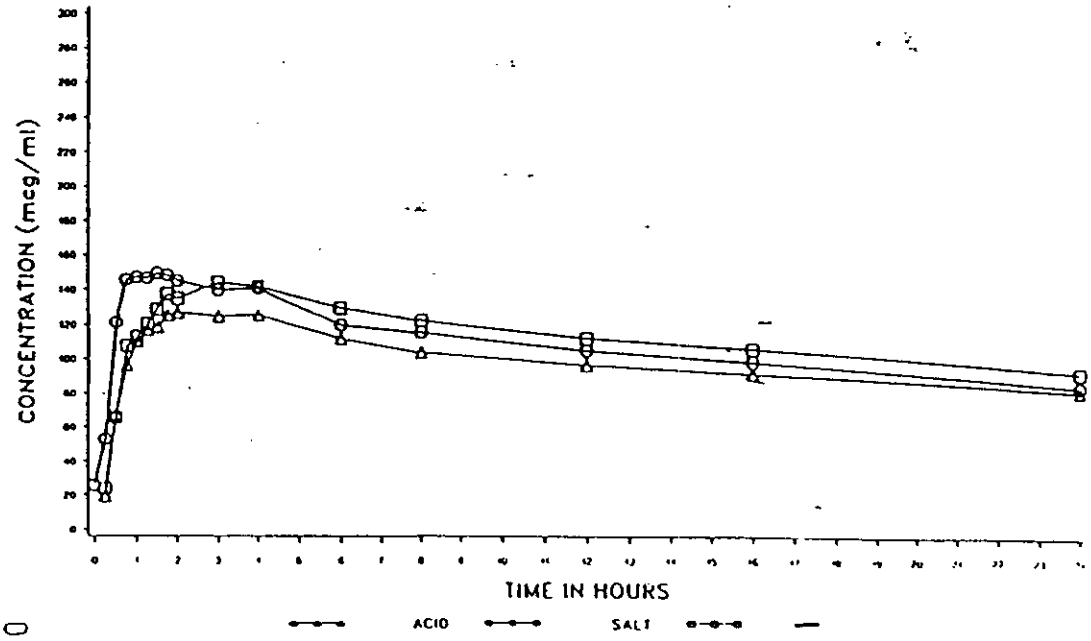


Steady-State Plasma Concentrations of Unbound Oxaprozin on Day 8 in 12 Healthy Subjects After Multiple Oral Doses of Oxaprozin 1200 mg Once Daily, Administered as Daypro (Oxaprozin Acid) (data from report no. N48-96-06-005).



PK PROFILE OF MULTIPLE ORAL DOSES OF OXAPROZIN (1200 MG QD)
N48-95-02-005

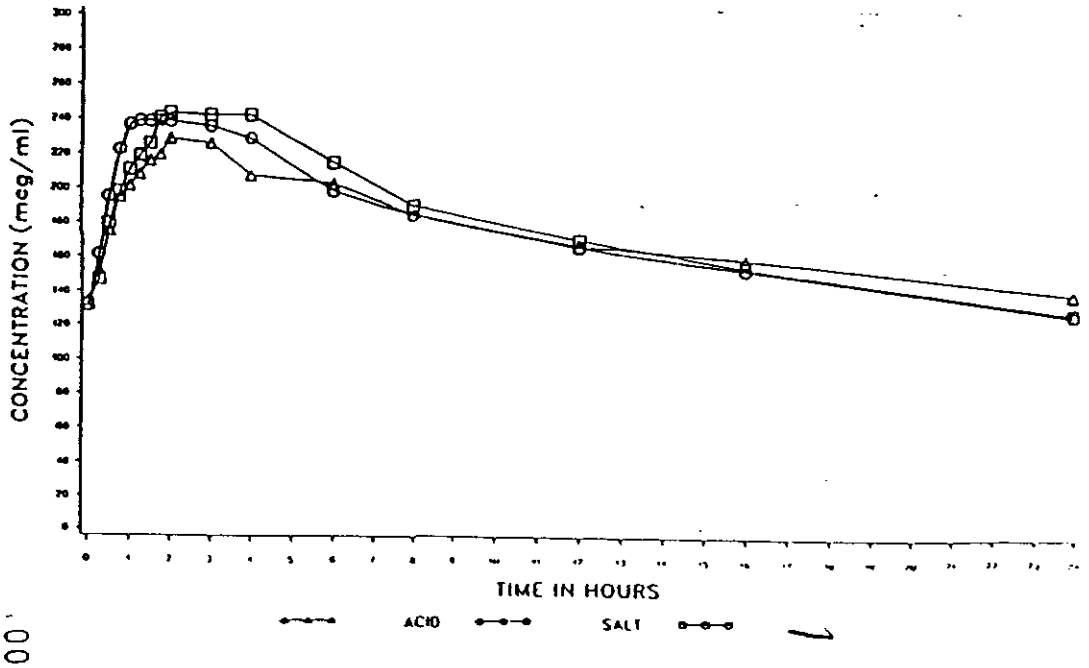
TOTAL MEAN PLASMA CONCENTRATION (mcg/ml) BY TIME
DAY 1



860

PK PROFILE OF MULTIPLE ORAL DOSES OF OXAPROZIN (1200 MG QD)
N48-95-02-005

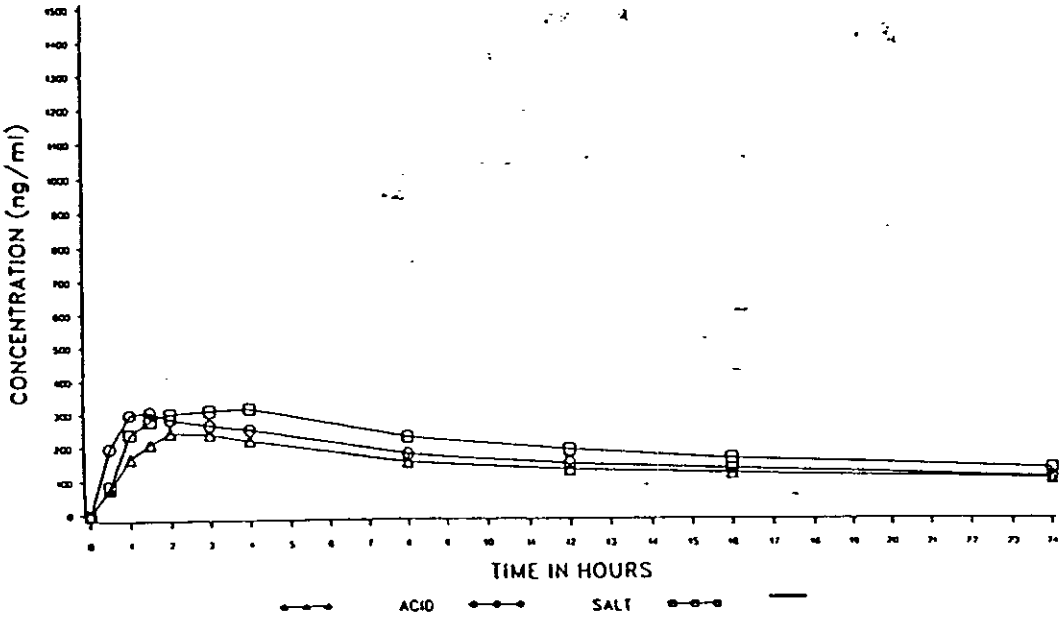
TOTAL MEAN PLASMA CONCENTRATION (mcg/ml) BY TIME
DAY 8



00

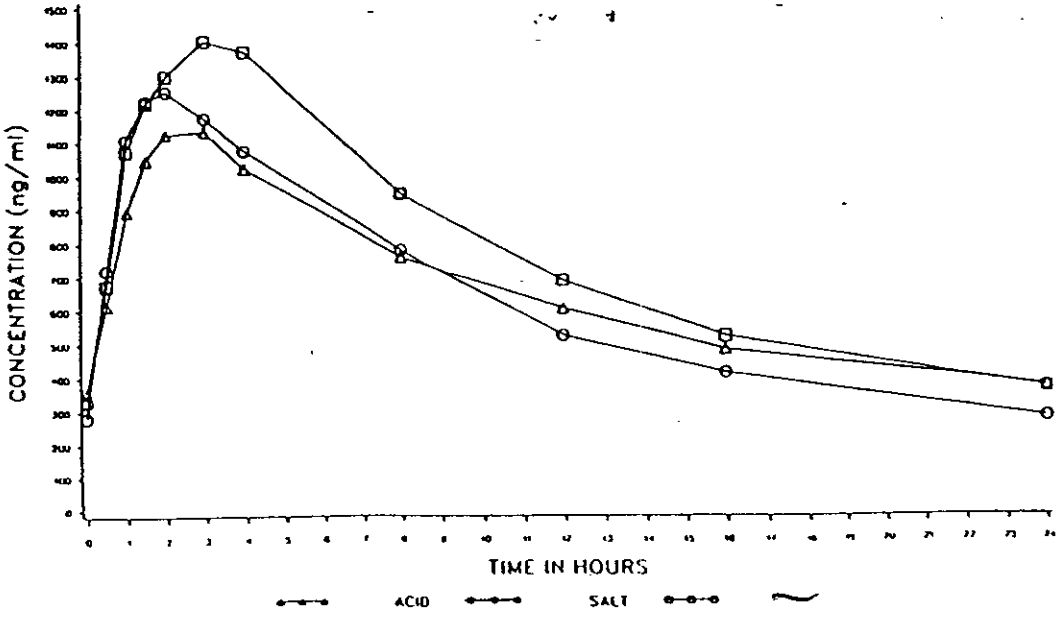
PK PROFILE OF MULTIPLE ORAL DOSES OF OXAPROZIN (1200 MG QD)
N48-95-02-005

UNBOUND MEAN PLASMA CONCENTRATION (ng/ml) BY TIME
DAY 1



PK PROFILE OF MULTIPLE ORAL DOSES OF OXAPROZIN (1200 MG QD)
N48-95-02-005

UNBOUND MEAN PLASMA CONCENTRATION (ng/ml) BY TIME
DAY 8



NDA #20-776 Submission Date: May 19,1997 Volumes: 1.11 & 1.12
Study Type: Food effect study Study # N48-96-02-013
Study Title: Effect of Food on the Bioavailability of Oxaprozin Potassium Tablets

Clinical Investigator: [redacted] Analytical Investigator [redacted]
Site: Site: [redacted]

Study Dates: 05 April 1996 - 23 April 1996

Study Design:
Single Dose: X Multiple Dose: Washout Period:
Cross-Over Parallel: X Other Design: Randomized: X

Fasted: All subjects fasted 8 hours Prior to dosing Post dosing:
Food Study: X Food Type: High fat breakfast (One slice of toasted white bread with butter, two fried eggs, two slices of bacon, two ounces of hash browned potatoes and eight ounces of whole milk.

Study Subjects: 48 healthy subjects were enrolled in the study and all 48 subjects completed the study.

Subject Breakdown

Subj. Type	Trt. Group	No. of Subj.	Male/ Female	Mean Age	Range	Mean Weight (kg)	Range (kg)
Healthy	Fed	24	19/5	27.5	19 - 45	72.8	54.5 - 96.0
Healthy	Fasted	24	17/7	22.8	18 - 42	70.0	52.5 - 89.0

Treatment Drug Product

Drug Product	Dose	Dosage Form	Strength	Packing Lot #	Mfg. Lot #	Expiration
Oxaprozin Potassium	2X600 mg	Tablet	600 mg	RCT 10054	PT-106-95*	June 1997

* - Registration lot

Sampling Times

Plasma: Blood samples for lithium determination were collected at0, 0.25, 0.5, 0.75, 1.0, 1.25, 1.50, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 144, 192, 240 hours after dose administration.

Assay Method: HPLC with UV detection was used for determination of oxaprozin (total oxaprozin at [redacted], unbound oxaprozin at [redacted]

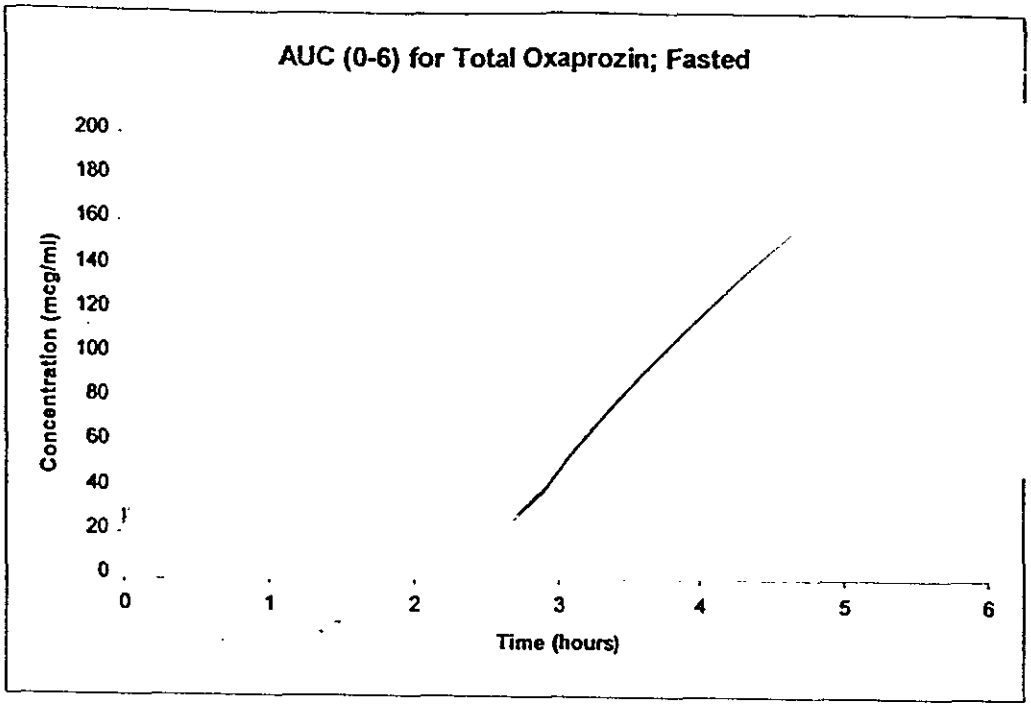
Assay Sensitivity: For total oxaprozin: [redacted] for unbound oxaprozin: [redacted]

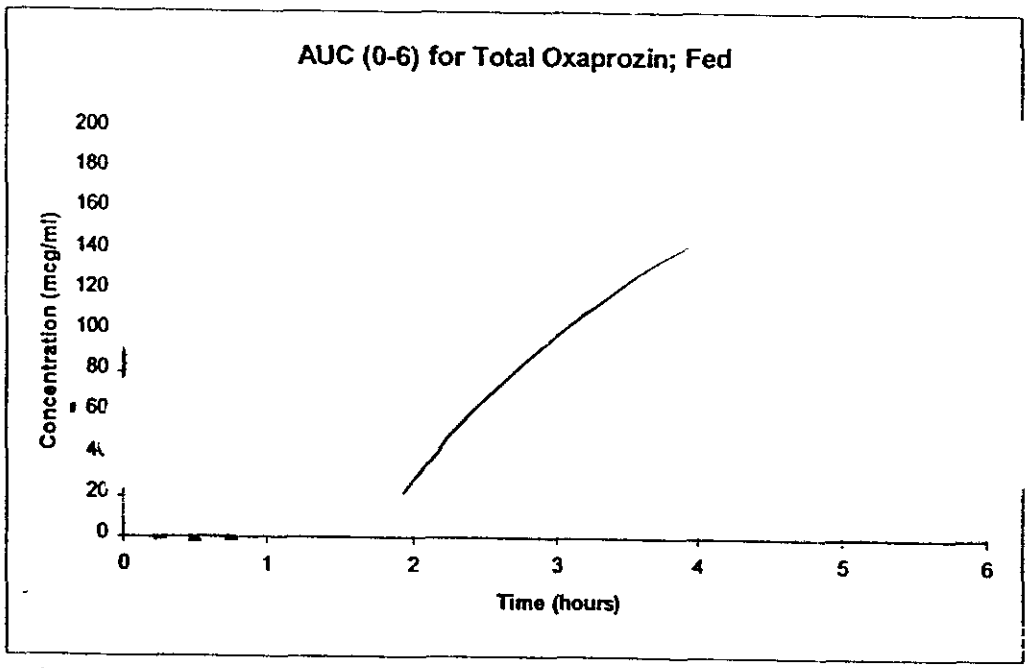
Assay Accuracy: %RE for total oxaprozin was from [redacted] to [redacted] for unbound oxaprozin (aqueous QC) was from [redacted]

Assay Precision: %RSD for total oxaprozin was from [redacted] for unbound oxaprozin was from [redacted]

Results:

Based on these results, it is apparent that the extent of absorption (AUC) was not significantly different between the fed and fasted state. However the presence of food delayed the time to reach the maximum concentration (T_{max}) for both the total and the unbound oxaprozin by about 36% and 28% respectively


AUC (0-6) for Total Oxaprozin; Fasted
Concentration (mcg/ml)
200
180
160
140
120
100
80
60
40
20
0
0
1
2
3
4
5
6
Time (hours)


AUC (0-6) for Total Oxaprozin; Fed
Concentration (mcg/ml)
200
180
160
140
120
100
80
60
40
20
0
0
1
2
3
4
5
6
Time (hours)

NDA # 20-776 Submission Date: May 19,1997 Volumes: 1.15 & 1.16
Study Type: Bioequivalence Study # N48-96-02-012
Study Title: Determination of Bioequivalence under Fasted Conditions of Oxaprozin Potassium Tablets Manufactured by Searle at Two Sites

Clinical Investigator:
Site:

Analytical Investigator
Site:

Study dates: 22, Mar. 1996 - 16, Apr. 1996

Study Objective: To determine the bioequivalence of 600mg oxaprozin potassium tablets manufactured at Searle's Mount Prospect, IL manufacturing site (reference tablet) versus 600mg oxaprozin potassium tablets manufactured at Searle's Caguas, Puerto Rico site (test tablet).

Study Design:
Single Dose: X Multiple Dose: Randomized: X Washout Period:
Cross-Over: Parallel: X Other Design:
Fasted: X Fed: Food Type:

Study Subjects: A total of fifty (50) healthy male and female subjects (25 in each group) were enrolled in this study, and forty eight (48) subjects completed the study. Two subjects (subject # 2 in group 1 & subject # 20 in group 2) were withdrawn from the study due to non-compliance with the protocol for blood collection and processing errors involving the one hour sampling time.

Subject Breakdown

Group #	No. of Subj.	Male/ Female	Mean Age (yr)	Range (yr)	Mean Weight (kg)	Range (kg)
1 (MP)	24	19 / 5	30.6	19 - 44	78.0	50.5 -107.0
2 (PR)	24	15 / 9	28.8	21 - 45	69.1	53.0 - 91.5

Drug Products

Drug Product	Dose	Dosage Form	Strength	Mfg. Site #	Mfg. Lot #	Batch Size*
oxaprozin potassium	1200 mg	Tabs	600 mg	MP, Illinois	TC-093-94	50,000
oxaprozin potassium	1200 mg	Tabs	600 mg	Puerto Rico	PT-106-95*	450,000

* - To-be-marketed formulation

Sampling Times

Plasma: Blood samples were collected at -0.25, 0, 0.25, 0.5, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 144, 193, and 240 hours after dose administration.

Assay Method: HPLC with UV detection was used for determination of total oxaprozin at ——— and unbound oxaprozin at ———

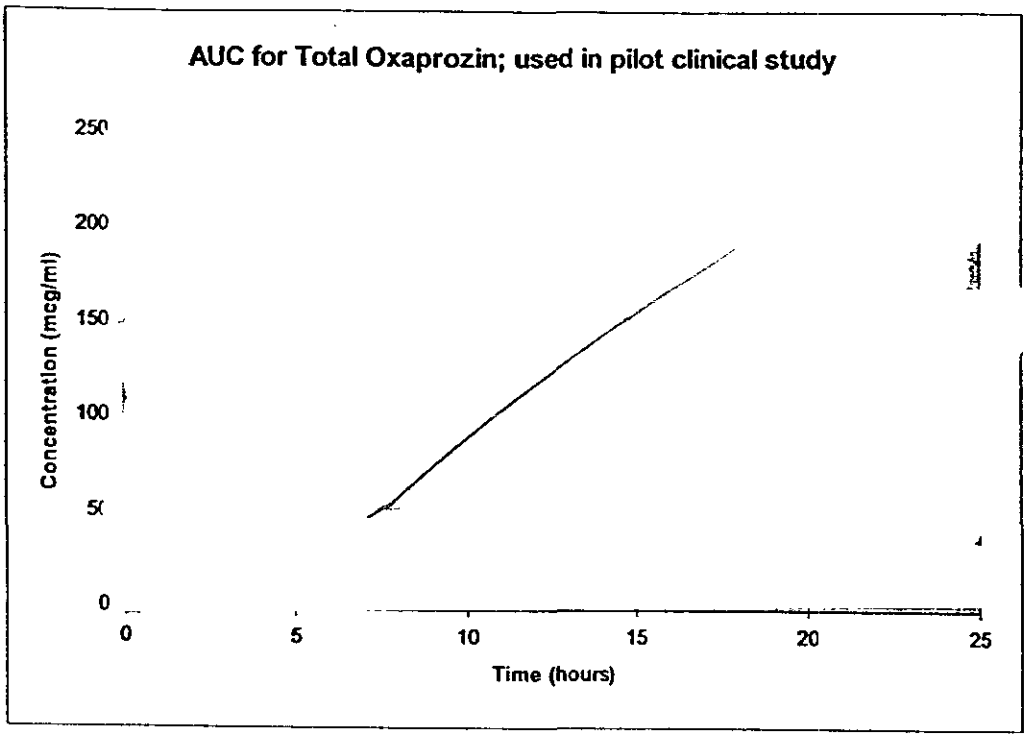
Assay Sensitivity: For total oxaprozin: ——— for unbound oxaprozin: ———

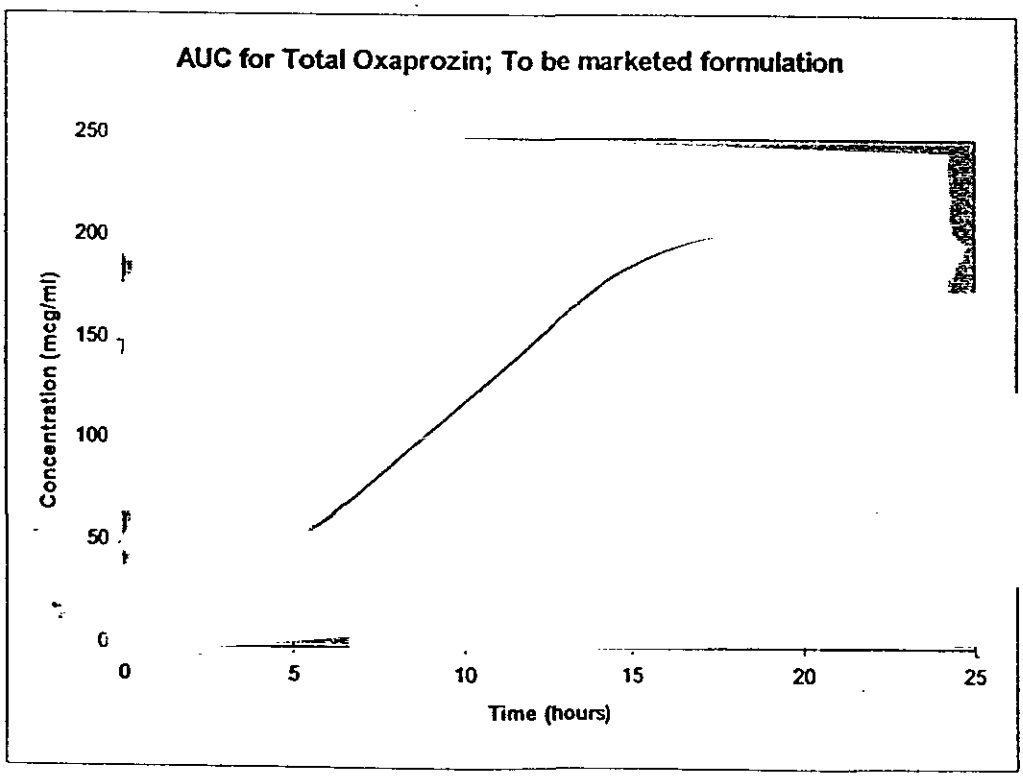
Assay Accuracy: %RE range for total from ——— for unbound (aqueous QC) from ———

Assay Precision: %RSD range for total from ——— for unbound from ———

Results:

The findings of this study indicates that the oxaprozin tablets manufactured in Puerto Rico is bioequivalent to the oxaprozin tablets manufactured in Illinois


AUC for Total Oxaprozin; used in pilot clinical study
250
200
150
100
50
0
Concentration (mcg/ml)
0
5
10
15
20
25
Time (hours)


AUC for Total Oxaprozin; To be marketed formulation
250
200
150
100
50
0
Concentration (mcg/ml)
0
5
10
15
20
25
Time (hours)