CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

13-217 / S-044

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

U.S. Food and Drug Administration
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation-III

Clinical Pharmacology & Biopharmaceutics Review

To:	Jane Dean, Project Manager, HFD-550
Through:	E. Dennis Bashaw, Pharm.D., DPE-III (HFD-880)
From:	Jang-Ik Lee, Pharm.D., Ph.D., DPE-III (HFD-880)
Date:	05/28/02
Re:	Metaxalone labeling revision (NDA 13-217 SLR044 Skelaxin Tablets 400 mg)

Metaxalone is a CNS depressant that has sedative and skeletal muscle relaxant effects. Metaxalone was approved in 1962 as an adjunct to rest, physical therapy and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The sponsor, Elan Pharmaceutical, submitted this NDA supplement to add the Pharmacokinetics section to current labeling based on the pharmacokinetic study report (No. AN151607) in which the effect of food on metaxalone absorption was provided. Dr. Moheb H. Makary at the Office of Generic Drugs (HFD-658) reviewed the study (see previous memorandum dated on 4/4/02). This reviewer concurred Dr. Makary's review and comments and recommended revising the proposed labeling by the sponsor (Attachment 1). The recommendation was sent to the sponsor through fax transmission on April 8, 2002 by the Project Manager. The sponsor disagreed with the recommendation and made a counter proposal (Attachment 2). This reviewer considered the sponsor's counter proposal and revised the labeling again with the addition of data and words for clarification as follows:

Pharmacokinetics

In a single center, randomized, two-period crossover study with 42 healthy volunteers (31 males, 11 females), a single 400mg Skelaxin (metaxalone) tablet was administered under both fasted and fed conditions. Under fasted conditions,

[redacted]

[redacted]

CC: HFD-550 (Villalba)
HFD-880 (Lazor)
HFD-880 (Selen)
HFD-650 (Conner)
HFD-658 (Makary)

Attachments: 1. Recommended labeling revision by the Agency
2. Counter-proposed labeling by the sponsor

Attachment 1

RECOMMENDED LABELING REVISION BY THE AGENCY

This revision was recommended by the reviewer (memorandum dated on 04/04/02) in response to the sponsor's initial proposal (N13-217 SLR044) and sent to the sponsor by the Project Manager thorough fax transmission (dated on 04/08/02).

~~ABC~~ suggests deletion of text and ABC does insertion of new text

Pharmacokinetics:

~~*Absorption:* A single center, single 400 mg dose of Skelaxin was administered in an open label, two-period (one fed and the other fasted), randomozed crossover study in 42 healthy volunteers (31 males, 11 females). At the 5% significance level, an analysis of variance (ANOVA) detected a statisticallly significant difference between treatments both in terms of maximal plasma concentrations (C_{max} fed: 1773.61 ng/mL plasma; fasted: 983.37 ng/mL) and extent of absorption of metxalone (AUC_{0-t} fed: 8439 ng-hr/mL plasma; fasted: 6961.81 ng-hr/mL plasma). For AUC_{inf}, a statistical difference was not noted(fed: 8541.31 ng-hr/mL; fasted 7478.90 ng-hr/mL)*.~~

~~[*The fed to fasted ratio of least-squares means for $AUC_{(0-t)}$, $AUC_{(inf)}$, and C_{max} were 121.23%, 114.21% and 180.36% respectively with corresponding confidence intervals of 113.43 – 129.03; 107.15-121.26 & 159.68-201.04]~~

[ ]

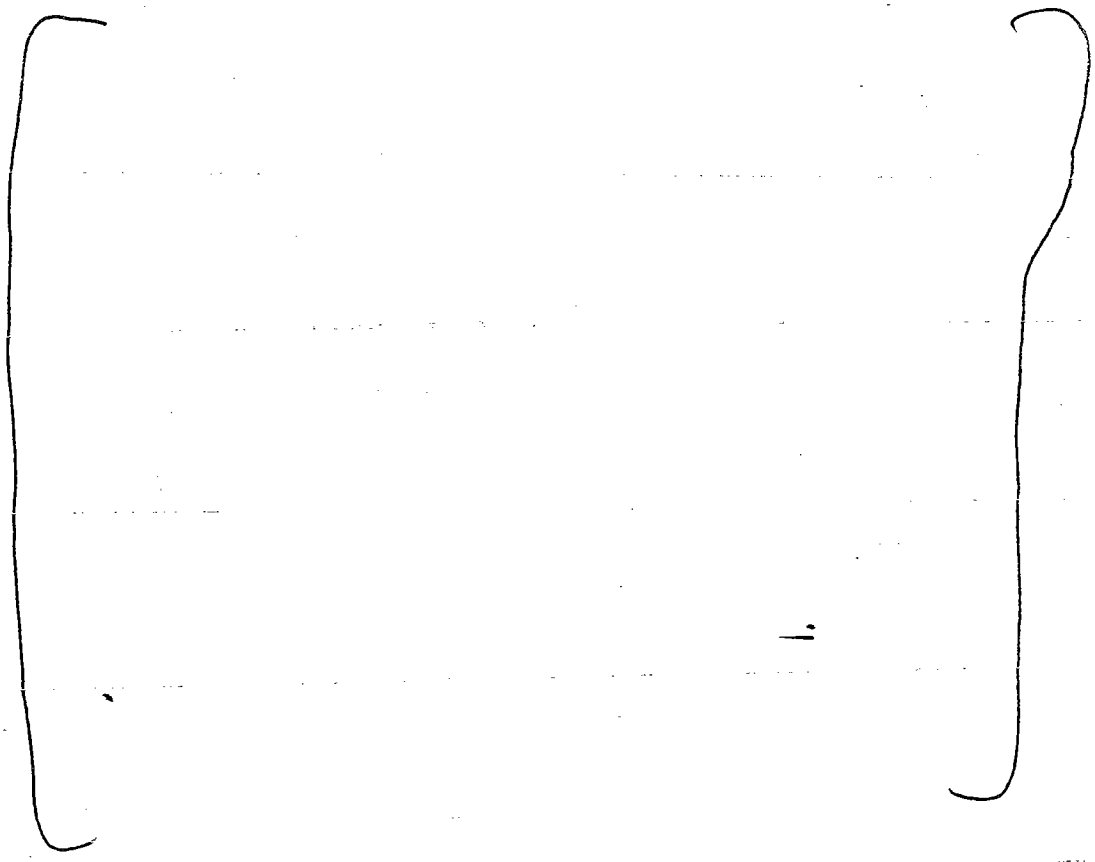
Attachment 2

COUNTER-PROPOSED LABELING BY THE SPONSOR

The sponsor made this counter-proposal for Skelaxin labeling (letter dated on 04/25/02) in response to the reviewer's recommendation transmitted through fax by the Project Manager (dated on 04/08/02).

Pharmacokinetics

In a single center, randomized, two-period crossover study with healthy volunteers (male and female subjects), a single 400 mg dose of SKELAXIN (metaxalone) was administered under fed and fasted conditions.



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

/s/

Jang-Ik Lee
5/28/02 05:27:57 PM
BIOPHARMACEUTICS
Revision considering sponsor's counter-proposal
Revision as of 5/28/02

Dennis Bashaw
5/28/02 05:38:44 PM
BIOPHARMACEUTICS

U.S. Food and Drug Administration
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation-III

Clinical Pharmacology & Biopharmaceutics Review

To:	Jane Dean, Project Manager, HFD-550
Through:	E. Dennis Bashaw, Pharm.D., DPE-III (HFD-880)
From:	Jang-Ik Lee, Pharm.D., Ph.D., DPE-III (HFD-880)
Date:	04/04/02
Re:	NDA 13-217 SLR044 Skelaxin (metaxalone) Tablets 400 mg

Metaxalone, a oxazolidinone derivative, is a CNS depressant that has sedative and skeletal muscle relaxant effects. Metaxalone was approved in 1962 as an adjunct to rest, physical therapy and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The sponsor, Elan Pharmaceutical, submitted this NDA supplement to revise the pharmacokinetics section to current labeling based on the pharmacokinetic study report (No. AN151607) in which the effect of food on metaxalone absorption was provided. The sponsor also submitted the same report in a citizen's petition requesting the Agency to expand the bioequivalence requirements for an approval of a generic version of metaxalone tablets to include the results of an acceptable food effect study. Thus, both Dr. Moheb H. Makary at the Office of Generic Drugs (HFD-658) and this reviewer at the Office of Clinical Pharmacology and Biopharmaceutics (HFD-880) reviewed the report.

The sponsor concluded in the report that the rate and extent of metaxalone absorption from currently marketed Skelaxin® Tablets were significantly increased when administered under fed conditions. In a randomized, two-period crossover study, a single dose of Skelaxin® 400 mg was administered to 42 healthy volunteers (31 males, 11 females) under fasted (10-hour overnight fast) and fed (standard high fat breakfast) conditions. The results show that the administration of Skelaxin® with food increased the log-transformed mean C_{max} and AUC_{last} of metaxalone to 177.5% (90% CI, 156.6 – 201.2%) and 123.5% (90% CI, 116.4 – 140.0%), respectively. The administration with food also increased mean T_{max} from 3.3 to 4.3 hr ($p = 0.022$) and shortened mean terminal half-life from 9.0 to 2.4 hr ($p < 0.001$). However, there was no significant change in AUC_{inf} (log-transformed mean to 114.4%; 90% CI, 109.2 – 121.8%).

In the review of the petition, Dr. Makary summarized the effect of food on metaxalone absorption (attachment). Dr. Makary agreed with the sponsor in that for an approval of a generic version of Metaxalone Tablets, 400 mg, an *in vivo* fed bioequivalence study in addition to an *in vivo* fasting bioequivalence is necessary to demonstrate the *in vivo* performance of generic metaxalone tablets.

This reviewer essentially agrees with Dr. Makary's review and comments. In addition, the following changes in the proposed package insert by the sponsor are recommended (~~ABC~~ suggests deletion of text and ABC does insertion of new text).

Pharmacokinetics:

~~*Absorption:* A single center, single 400 mg dose of Skelaxin was administered in an open label, two period (one fed and the other fasted), randomozed crossover study in 42 healthy volunteers (31 males, 11 females). At the 5% significance level, an analysis of variance (ANOVA) detected a statisticallly significant difference between treatments both in terms of maximal plasma concentrations (C_{max} fed: 1773.61 ng/mL plasma; fasted: 983.37 ng/mL) and extent of absorption of metxalone (AUC_{0-t} fed: 8439 ng-hr/mL plasma; fasted: 6961.81 ng-hr/mL plasma). For AUC_{inf}, a statistical difference was not noted(fed: 8541.31 ng-hr/mL; fasted 7478.90 ng-hr/mL)*.~~

~~[*The fed to fasted ratio of least squares means for $AUC_{(0-t)}$, $AUC_{(inf)}$, and C_{max} were 121.23%, 114.21% and 180.36% respectively with corresponding confidence intervals of 113.43 – 129.03; 107.15-121.26 & 159.68-201.04]~~

In a single center, randomized, two-period crossover study with 42 healthy volunteers (31 males, 11 females), a single dose of Skelaxin® Tablet 400 mg was administered under fasted and fed conditions. Under fasted conditions,

CC: HFD-550 (Villalba)
HFD-880 (Lazor)
HFD-880 (Selen)
HFD-650 (Conner)
HFD-658 (Makary)

Attachment: Review of a Citizen Petition

Metaxalone
400 mg Tablet
Control #01-525
Reviewer: Moheb H. Makary
W 01525C.O01/01P-0481/CP1

Elan Pharmaceuticals
Ceder Knolls, NJ
Submission Date:
October 16, 2001

Review of a Citizen Petition

I. Objective:

The firm submitted this citizen petition requesting the FDA to expand the bioequivalence requirements for approval of a generic version of Metaxalone Tablets to include the results of an acceptable food effect study.

In support of its request, Elan Pharmaceutical submitted the results of an *in vivo* food effect study on Skelaxin^{R} (metaxalone) 400 mg administered with and without food to healthy volunteers.

In addition, concurrently with the filing of this petition Elan has submitted a labeling supplement to the Skelaxin^{R} NDA (No. 13217) to revise the labeling to reflect the results of this study.

The petitioner is aware of the March 6, 2001 petition filed by URL Mutual Pharmaceutical Co. Inc. (Docket No.01P-0117/CP1) requesting that the FDA require an acceptable *in vivo* fasting bioequivalence study demonstrating that the generic product and the reference product are bioequivalent as a condition of approval of a generic version of Skelaxin^{R} (metaxalone) Tablets, 400 mg.

II. Background:

Metaxalone, an oxazolidinone derivative, is a central nervous system depressant that has sedative and skeletal muscle relaxant effects. The precise mechanism of action of the drug is not known. When administered orally, its skeletal muscle relaxant effects are minimal and are probably related to its sedative effect. The plasma concentrations required for pharmacologic action of metaxalone are not known. A single, oral 800-mg dose of metaxalone produces mean peak levels of 296 ng/mL in 2 hours. The onset of action is usually within 1 hour and the duration of action is about 4-6 hours. The drug has a plasma half-life of 2-3 hours. Metaxalone is metabolized by the liver and excreted in urine as unidentified metabolites.

Metaxalone was first approved in 1962 and is currently marketed by Elan as Skelaxin® tablets in 400 mg strength. Prior to Mutual's Citizen Petition, the Office of Generic Drugs (OGD) informed inquiring firms that since metaxalone is a DESI effective drug, the Agency asked applicants to a request a waiver of *in*

vivo bioequivalence study requirements along with acceptable in vitro dissolution profiles to meet ANDA bioequivalence approval criteria under 21 CFR 320.22(c).

On March 6, 2001, URL Mutual Pharmaceutical Company submitted a Citizen Petition requesting that the FDA rescind a previous determination that metaxalone tablets is a drug product not presenting bioequivalence problems and announce publicly in the *FDA's Approved Drug Products with Therapeutic Equivalents* (Orange Book) that an *in vivo* fasting bioequivalence study will be required as a condition of approval of any ANDA for a generic version of a solid oral dosage form of metaxalone. The petitioner also requested that the Office of Generic Drugs (OGD) not approve any ANDA for a generic version of metalaxone that does not contain the results of an acceptable *in vivo* fasting bioequivalence study. To support these assertions, the petition included results of two *in vivo* bioequivalence fasting studies and *in vitro* dissolution testing.

Following a review of URL Mutual's Citizen Petition by the Division of Bioequivalence, Office of Generic Drugs, the Agency published a proposal in the Orange Book to change the designation for metaxalone tablets from a "non bioproblem" to a "bioproblem" drug. This change in designation recognizes that there is no defined in *vivo/in vitro* correlation, thus an in vivo bioequivalence fasting study is necessary to demonstrate the *in vivo* bioequivalence of metaxalone tablets.

Currently, the Agency has initiated a process whereby it proposes to notify industry of the need for an *in vivo* fasting study as a condition of ANDA approval.

III. Following is a summary and the OGD response to the statement of grounds.

Based on the results of a pharmacokinetics study showing a marked food effect on metaxalone, Elan is requesting that the abbreviated new drug application approval requirements be further modified to include acceptable bioequivalence to the reference product when administered under both the fed and fasting conditions.

On July 2001, Elan initiated a study to determine if food has an effect on Skelaxin^R absorption. A single 400 mg dose of Skelaxin^R was administered under fasting (10-hour overnight fast) and fed (standard high fat breakfast) conditions in a two treatment, randomized, crossover study in 42 healthy volunteers (31 males and 11 females). The results indicate that the bioavailability was significantly increased when Skelaxin^R was administered with food in that both the rate (C_{max}) and extent of absorption (AUC_{0-t}) were increased. There was no significant difference noted for AUC_{inf}. The Division of Bioequivalence concurs with this conclusion. [A detailed review of Study #AN151607 is attached].

The draft CDER Guidance for Industry Guidance for Industry *Food-Effect Bioavailability and Fed Bioequivalence Studies Study Design, Data Analysis and*

Labeling, states that a food effect on bioavailability is indicated if the 90% confidence interval for the ratio of population geometric means between fed and fasted treatments is not contained in the equivalence limits of 80%-125% for either AUC_{inf}, (AUC_{0-t}) or C_{max}. Based on these criteria, Elan's study #AN151607 showed that food has a significant effect on metaxalone pharmacokinetics. AUC_{0-t} and C_{max} failed to meet the 90% CI limits of 80-125% and the C_{max} value was 80% higher under fed compared to fasting conditions.

It is the current policy of the Agency to request that generic firms conduct a fed bioequivalence study if there is a significant effect of food on drug pharmacokinetics (unless the product should be taken only on an empty stomach or is considered BCS Class I). Thus, the Agency agrees that for approval of a generic version of Metaxalone Tablets, 400 mg, an *in vivo* fed bioequivalence study in addition to an *in vivo* fasting bioequivalence is necessary to demonstrate the *in vivo* bioequivalence of metaxalone tablets.

Moheb H. Makary, Ph.D. Date:
Review Branch III
Division of Bioequivalence

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT_____ Date

Concur:_____ Date:
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/ 10-31-01, 12-14-01, 12-18- 01, 015252C.O01
cc: ANDA #01-525, original, HFD-658 (Makary), Drug File, Division File.

Attachment 1:

Review of a Study Submitted to Support Citizen Petition 01P-0481/CP1

Protocol No.: AN151607, Bioavailability Study of Skelaxin^{R} (Metaxalone) 400 mg Administered With and Without Food To Healthy Volunteers

STUDY FACILITY INFORMATION

CLINICAL FACILITY: [redacted]
CLINICAL STUDY DATE: Period I: 7/21 – 7/22, 2001; Period II: 7/28 – 7/29, 2001
ANALYTICAL FACILITY: [redacted]
PRINCIPAL INVESTIGATOR: [redacted]
ANALYTICAL STUDY DATES: 7/31 – 8/10, 2001

TREATMENT INFORMATION

	A	B
TREATMENT ID:	A	B
TEST OR REFERENCE:	T	R
PRODUCT NAME:	Skelaxin®	Skelaxin®
MANUFACTURER:	West-Ward Pharmaceutical Corp	West-Ward Pharmaceutical Corp
MANUFACTURE DATE:	02/2001	02/2001
EXPIRATION DATE:	02/2003	02/2003
STRENGTH:	400 mg	400 mg
DOSAGE FORM:	Tablet	Tablet
LOT NO.:	SKLWW263F	SKLWW263F
BATCH SIZE:	N/A	N/A
ASSAY:	N/A	N/A
CONTENT UNIFORMITY:	N/A	N/A
DOSE ADMINISTERED:	1 x 400 mg	1 x 400 mg
STUDY CONDITION:	Nonfasting (Fed Conditions)	Fasting
LENGTH OF FASTING:	Breakfast was given 30 minutes prior to dosing	10 hours

RANDOMIZATION		**DESIGN**	
RANDOMIZED:	Y	DESIGN TYPE:	Crossover
NO. OF SEQUENCES:	2	BALANCED:	Y
NO. OF PERIODS:	2	WASHOUT PERIOD:	7 days
NO. OF TREATMENTS:	2		

Randomization Scheme:

AB	2, 5, 12, 14, 16, 17, 18, 21, 23, 24, 26, 27, 29, 30, 31, 36, 37, 39, 40, 41, 43
BA	3, 4, 6, 7, 8, 9, 11,13,15,19, 20, 22, 25, 28, 32, 33, 34, 35, 38, 42, 44

Subjects # 01 and #10 were dropped by the investigator prior to period II dosing. Subject #1 was unable to

DOSING	consume scheduled breakfast prior to period II dosing. Subject #10 was dropped due to positive drug abuse screen prior to period II dosing.
SINGLE OR MULTIPLE DOSE:	Single
VOLUME OF LIQUID INTAKE:	240 ml
ROUTE OF ADMINISTRATION:	Oral
Blood Sampling Schedule	Pre-dose (0 h), 0.5,1,1.5,2.0,2.5,3.0,3.5,4.0, 4.5, 5.0,6.0, 8.0, 12.0, 16.0, 24.0 and 36.0 hours, post-dose.
SEX(ES) INCLUDED:	31 Male, 13 female
HEALTHY VOLUNTEERS ONLY:	Y
NO. OF ADVERSE EVENTS:	A total of 18 adverse events were reported by 13 subjects. Four adverse events were considered unrelated by the investigator and 14 adverse events were considered related to the study drug.

Demographic profile of subjects in Study #AN151607

CRO : [redacted]

Age

Mean:	23.5 years
SD:	5.7
Range:	18-42 years

Groups	%	No. of Subjects
< 18	0%	0
18 - 40	97.7%	43
41 - 64	2.3%	1
65 - 75	0%	0
> 75	0%	0
Gender		
Male	70.5%	31
Female	29.5%	13
Race		
Asian	2.3%	1
African American	4.5%	2
Hispanic	2.3%	1
Caucasian	86.4%	38
Other	4.5%	2

PRE-STUDY ASSAY VALIDATION INFORMATION

	Metaxalone
ANALYTE:	
ASSAY METHOD:	
MATRIX:	
INTERNAL STANDARD:	
SENSITIVITY/LOQ:	
STANDARD CURVE	
QC SAMPLES	
r^2 IS GREATER THAN	
SPECIFICITY:	
INTER-DAY ACCURACY(%)[STD]	
INTER-DAY PRECISION(%CV)[STD]	
INTRA-DAY ACCURACY(%)[QC]	
INTRA-DAY PRECISION (%CV)[QC]	
INTER-DAY ACCURACY(%)[QCs]	
INTER-DAY PRECISION(CV%)[QCs]	
MEAN % RECOVERY	
INT. STD RECOVERY (%)	
STABILITY (QCs):	
Long-term at -20° C	
Freeze-Thaw Cycles	

Within-Study Assay Results:

Assay method, biological matrix, and internal standards were similar to those of pre-study method validation.

	Metaxalone
ANALYTE:	
SENSITIVITY	
STANDARD CURVE RANGE:	
QC Samples	
INTER-DAY ACCURACY (%)[QC]	
INTER-DAY PRECISION (% CV) [QC]	

Sample Reassays: The total number of repeats represents 2.2% of the overall number of samples for metaxalone. There were no pharmacokinetic repeats.

PHARMACOKINETIC / STATISTICAL ANALYSES

METAXALONE Pharmacokinetic Parameters (n = 42)
Treatment A, 400mg tablets, Dose Administered = 1 x 400 mg Skelaxin®, nonfasting
Treatment B = Skelaxin®, 400 mg tablets, Dose Administered = 1 x 400 mg, fasting

Mean Plasma concentrations and PK Parameters are shown below:

TIME (HR)	FED TREATMENT A (ng/mL)		FASTED TREATMENT B (ng/mL)	
0	0.00		0.00	
0.5	61.60	(240)	50.94	(148)
1	335.66	(216)	192.40	(125)
1.5	633.91	(153)	355.37	(118)
2	938.91	(108)	526.83	(94.1)
2.5	1136.09	(82.0)	676.62	(75.2)
3	1192.89	(65.8)	734.68	(67.4)
3.5	1256.30	(58.3)	753.79	(64.1)
4	1252.01	(52.5)	797.37	(62.5)
4.5	1276.77	(50.5)	834.86	(61.1)
5	1169.82	(52.4)	767.75	(58.1)
6	851.44	(66.9)	555.98	(59.3)
8	430.76	(92.2)	321.41	(61.1)
12	153.33	(141)	163.69	(72.1)
16	50.51	(150)	101.65	(58.7)
24	14.07	(221)	81.62	(59.0)
36	0.99	(396)	21.62	(103)

Mean plasma concentrations are presented in Figure 1.

Parameter	Treatment A Fed	(%CV)	Treatment B Fasted	(%CV)	A/B Ratio
		(A)	(B)	(B)	(A)/(B)
AUC_{0-T}	8439.62	48.5	6961.81	52.5	1.23
AUC_{INF}	8541.31	48.1	7478.90	50.6	1.15
C_{MAX}	1773.61	51.0	983.37	52.6	1.78
T_{MAX}	4.29		3.32		
K_{el}	0.3436		0.0971		
T_{HALF}	2.37		9.04		

UNIT: AUC = ng.hr/mL C_{MAX} = ng/mL T_{MAX} = hr

	90% CI
LnAUC(0-t)	116.4-130.9%
LnAUCinf	109.2-121.8%
LnCmax	156.6-201.2%

1. For metaxalone, the mean AUC(0-t), AUCinf and Cmax values were 17.5%, 14.2% and 80.4% higher, respectively, under fed conditions compared with fasting conditions. The ANOVA showed a statistically significant treatment (food) effect for all three parameters, AUCinf, AUC(0-t), and Cmax ($P < 0.001$).

2. The draft CDER Guidance for Industry, *Food-Effect Bioavailability and Fed Bioequivalence Studies Study Design, Data Analysis and Labeling,* states that a food effect on bioavailability is indicated if the 90% confidence interval (CI) for the ratio of population geometric means (fed/fasted) is not contained in the equivalence limits of 80-125% for either AUCinf, (AUC0-t) or Cmax. The 90% CIs were not within the acceptable range of 80-125% for log-transformed AUC(0-t) and Cmax. The 90% confidence intervals for Cmax were completely outside of the 80-125% range. The ratios of the geometric means (expressed as a percentage) were within this range for AUC(0-t) and AUCinf and outside of this range for Cmax. The reviewer's calculations are similar to those submitted by the firm.

3. There was no pattern of the food effect between males and females. Food increased Cmax values in all subjects except for subjects 3, 13, 17, 23, and 33 (two females and three males). Food increased AUC(0-t) values in all subjects except for subjects 2, 3, 26, 27, 29, 33 and 36 (three females and four males). The most marked changes in Cmax (3- to 4-fold) were observed in subjects 5, 6, 14, 22, 37, and 43 (two females and four males). The most marked changes in AUC(0-t) (about 2-fold) were observed in subjects 4, 38, and 43 (two females and one male) (See Figures 2 and 3).

4. Under fed conditions, the mean T1/2 value of metaxalone was about one-fourth the value under fasting conditions.

5. There were no differences in the adverse event profiles between the two treatment groups (see Attachment II).

6. Thus, in Study AN151607, AUC(0-t) and Cmax failed to meet the 90% CI limits of 80-125% and the Cmax value was 80% greater in fed compared to fasting conditions for this food-effect bioavailability study. The Division of Bioequivalence concludes that this study demonstrated a marked food effect on metaxalone pharmacokinetics.

7. The Division of Bioequivalence concurs with the action requested by the petitioner. The FDA should request, as a condition for approval, that an ANDA for a generic version of Skelaxin^{R} (metaxalone) tablets should include an acceptable fed bioequivalence study comparing the generic product to the reference listed drug.

Figure 1

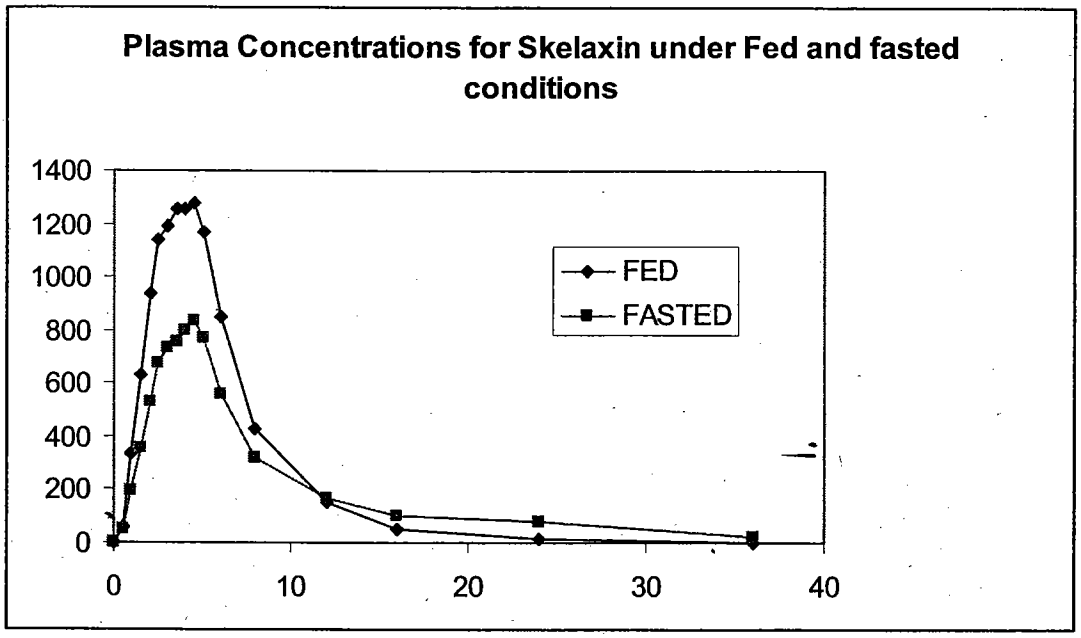

Plasma Concentrations for Skelaxin under Fed and fasted conditions
1400
1200
1000
800
600
400
200
0
0
10
20
30
40
FED
FASTED

Figure 2: Comparison of individual metaxalone Cmax values in fed vs fasted subjects

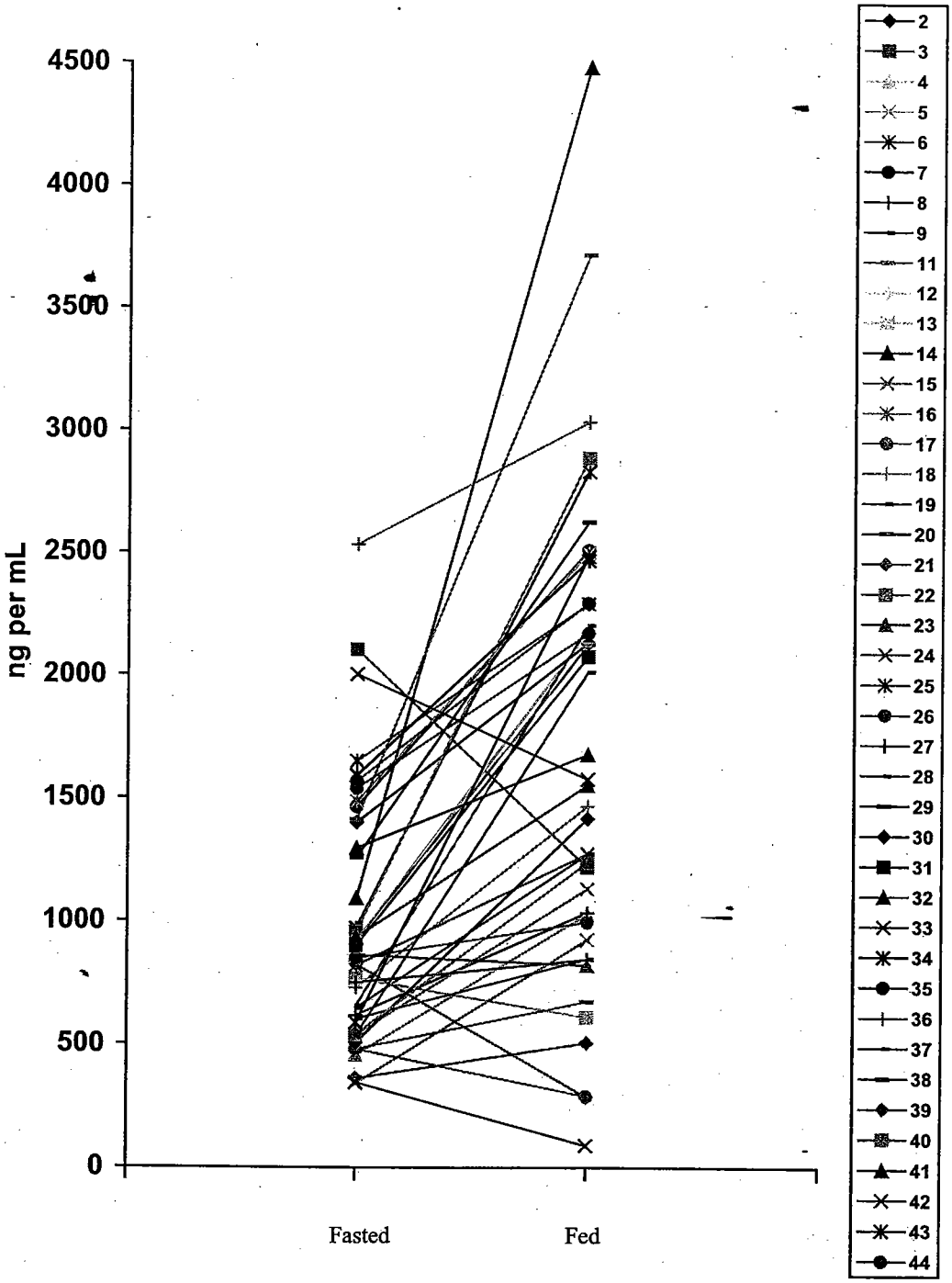
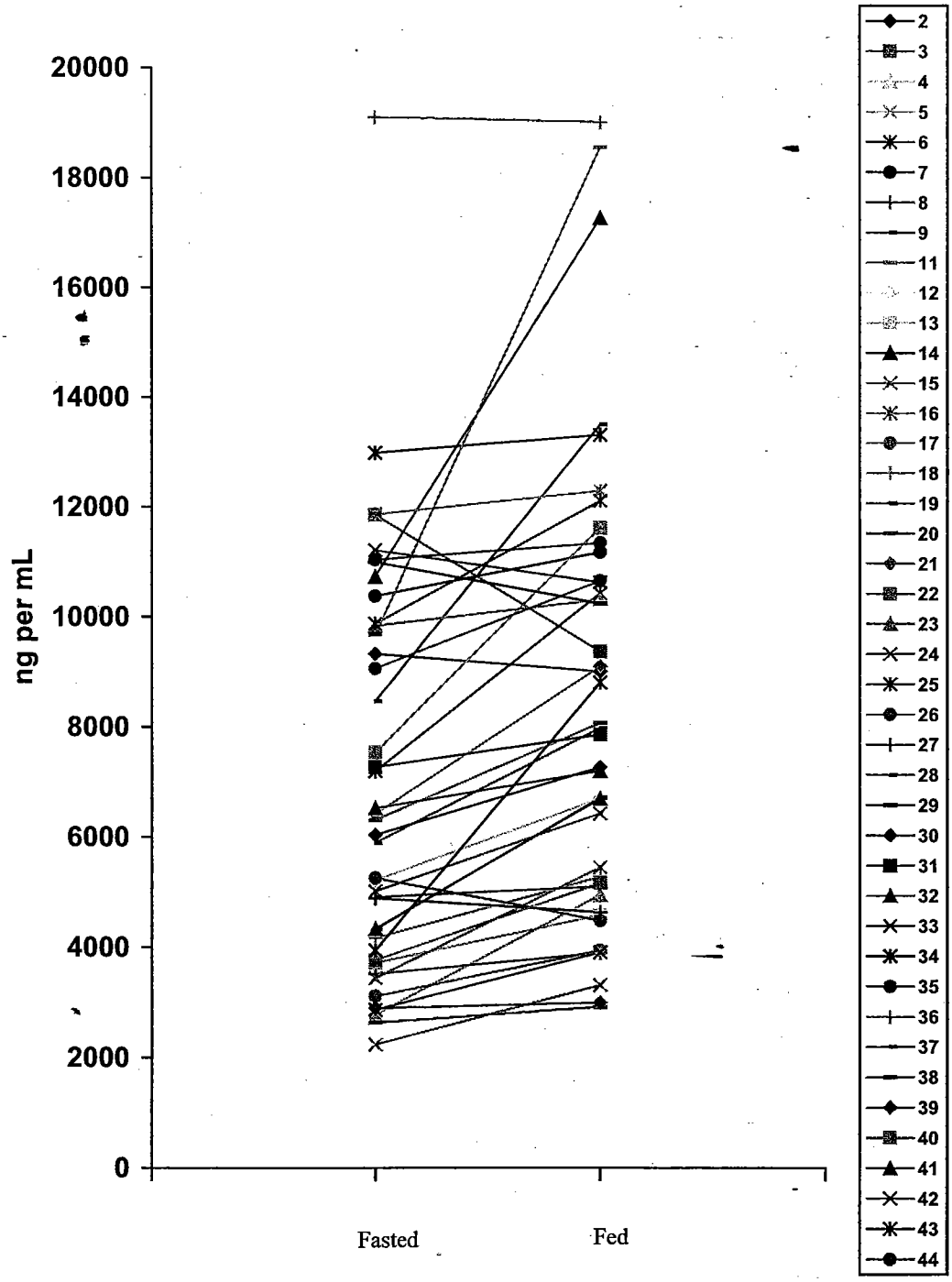


Figure 3: Comparison of individual metaxalone AUCt values in fed vs fasted subjects



Attachment II

Adverse Events: Number of Observed and Rate, with Subject Identification

Treatment A: Skelaxin[R] administered with Food

Event	Mild		Moderate		Severe		Total		Total
	Related	NR	Related	NR	Related	NR	Related	NR	
Headache	2 (25%) 17 34	1 (13%) 36							3
Nausea	1 (13%) 33								1
Pain Abdomen (Stomachache)	1(13%) 43								1
Pain Chest	1(13%)								1
Stomatitis Ulcer (Canker Sore)		1 (13%) 26							1
Vomit	1(13%) 34								1

(%) Denotes the percent of total adverse events within treatment.

Treatment A: Skelaxin[R] administered without Food

Event	Mild Related	Mild NR	Moderate Related	Moderate NR	Severe Related	Severe NR	Total Related	Total NR	Total
Headache	7 (70%) 12 15 17 33 35 35 38								7
Cold Sore Top Right Lip		1 (10%) 06							1
Dyspepsia Ulcer (Heartburn)	1 (10%) 22								1
Pain Abdomen (Stomachache)	1(10%) 20								1

(%) Denotes the percent of total adverse events within treatment.

CC: Control #01-525
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit

V:\FIRMSAM\ELAN\CONTROLS\01525C.O01
Printed in final on 12/18/01

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit
HFD-650/ D. Conner

BIOEQUIVALENCY - ACCEPTABLE submission date:10/16/01

1. **OTHER** (OTH)Control

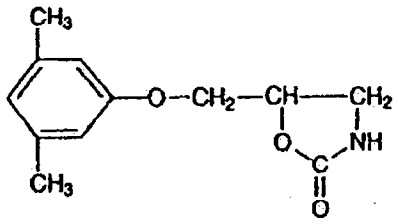
Outcome: AC

Outcome Decisions: **AC** – Acceptable

SKELAXIN® (Metaxalone)

Description: Each pale rose, scored tablet contains: metaxalone, 400 mg.

Skelaxin® (Metaxalone) has the following chemical structure and name:



5-[(3,5-dimethylphenoxy) methyl]-2-oxazolidinone

Actions: The mechanism of action of metaxalone in humans has not been established, but may be due to general central nervous system depression. It has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.

Indications: Skelaxin® (metaxalone) is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Metaxalone does not directly relax tense skeletal muscles in man.

Pharmacokinetics:

Absorption: A single center, single 400 mg dose of Skelaxin was administered in an open label, two-period (one fed and the other fasted), randomized crossover study in 42 healthy volunteers (31 males, 11 females). At the 5% significance level, an analysis of variance (ANOVA) detected a statistically significant difference between treatments both in terms of maximal plasma concentrations (C_{max} fed: 1773.61 ng/mL plasma; fasted: 983.37 ng/mL) and extent of absorption of metaxalone (AUC_{0-t} fed: 8439.62 ng-hr/mL plasma; fasted: 6961.81 ng-hr/mL plasma). For AUC_{inf}, a statistical difference was not noted (fed: 8541.31 ng-hr/mL; fasted: 7478.90 ng-hr/mL)*.

[*The fed to fasted ratio of least-squares means for $AUC_{(0-t)}$, $AUC_{(inf)}$, and C_{max} were 121.23%, 114.21% and 180.36%, respectively with corresponding 90% confidence intervals of 113.43 – 129.03; 107.15-121.26 & 159.68-201.04]

Contraindications: Metaxalone is contraindicated in individuals who have shown hypersensitivity to the drug. Metaxalone should not be administered to patients with a known tendency to drug induced, hemolytic, or other anemias. It is contraindicated in patients with significantly impaired renal or hepatic function.

Precautions: Elevation in cephalin flocculation tests without concurrent changes in other liver function parameters have been noted. Hence it is recommended that metaxalone be administered with great care to patients with pre-existing liver damage and that serial liver function studies be performed as required.

False-positive Benedict's tests, due to an unknown reducing substance, have been noted. A glucose-specific test will differentiate findings.

Pregnancy: Reproduction studies have been performed in rats and have revealed no evidence of impaired fertility or harm to the fetus due to metaxalone. Reactions reports from marketing experience have not revealed evidence of fetal injury, but such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus. Safe use of metaxalone has not been established with regard to possible adverse effects upon fetal development. Therefore, metaxalone tablets should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgement of the physician the potential benefits outweigh the possible hazards.

Nursing Mothers: It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use: Safety and effectiveness in children 12 years of age and below have not been established.

Adverse Reactions: The most frequent reactions to metaxalone include nausea, vomiting, gastrointestinal upset, drowsiness, dizziness, headache, and nervousness or "irritability." Other adverse reactions are: hypersensitivity reaction, characterized by a light rash with or without pruritus; leukopenia; hemolytic anemia; jaundice.

Dosage: The recommended dose for adults and children over 12 years of age is two tablets (800 mg) three to four times a day.

Management of Overdosage: Gastric lavage and supportive therapy as indicated. (When determining the LD_{50} in rats and mice, progressive sedation, hypnosis and finally respiratory failure were noted as the dosage increased. In dogs, no LD_{50} could be determined as the higher doses produced an emetic action in 15 to 30 minutes). No documented case of major toxicity has been reported.

How Supplied: Skelaxin® (metaxalone) is available as a 400 mg pale rose tablet, inscribed with 8662 on the scored side and "C" on the other. Available in bottles of 100 (NDC 0086-0062-10) and in bottles of 500 (NDC 0086-0062-50).

Store at Controlled Room Temperature, between 15° C and 30° C (59° F and 86° F).

Rx Only

The most recent revision of this labeling is October 2000.

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

/s/

Jang-Ik Lee
4/4/02 01:58:15 PM
BIOPHARMACEUTICS
Labeling recommendation needs to be communicated with the sponsor

Added CL/F 53.5 L/hr, Attached OGD review and PI to the memo

Dennis Bashaw
4/4/02 04:03:42 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 13-217/S-044

Elan Pharmaceuticals
Attention: Linda Ballai Fischer
Director, Regulatory Affairs
45 Horse Hill Road
Cedar Knolls, NJ 07927

Dear Ms. Fischer:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Skelaxin, (metaxalone tablets) Tablet, 400mg

NDA Number: 13-217

Supplement number: S-044

Date of supplement: October 16, 2001

Date of receipt: October 17, 2001

This supplemental application proposes the addition of a supplement pharmacokinetics section to the package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 16, 2001, in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products, HFD-550
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products, HFD-550
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, please contact Ms. Jane A. Dean, Regulatory Project Manager, at (301) 827-2090.

Sincerely yours,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Lori Gorski
12/21/01 11:33:18 AM
Lori Gorski has signed for Carmen DeBellas