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CV 03 0006

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DEARIE, J.

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK

ELAN PHARMACEUTICALS, INC.,	)	
	)	
Plaintiff	)	
	)	Case No.:
v.	)	
	)	
EON LABS, INC.,	)	
	)	
Defendant.	)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Elan Pharmaceuticals, Inc. ("Elan"), by its undersigned counsel, brings this action for patent infringement against Defendant Eon Labs, Inc. ("Eon"). This action relates to a patent covering a method for increasing the bioavailability of the drug metaxalone by administering it with food. Elan alleges as follows:

1. Elan is a Delaware corporation having its corporate offices and principal place of business at 800 Gateway Boulevard, South San Francisco, California 94080. Elan is engaged in the business of researching, developing, manufacturing and selling pharmaceutical products throughout the world.

2. Upon information and belief, Eon is a Delaware Corporation having a place of business at 227-15 N. Conduit Avenue, Laurelton, New York 11413. Upon information and belief, Eon is engaged in the business of preparing generic prescription pharmaceuticals for distribution in New York and throughout the United States.

3. This patent infringement action arises under 35 U.S.C. §§ 271(e) and 281-283. Subject matter jurisdiction is proper under 28 U.S.C. §§ 1331 and 1338(a). Venue is proper under 28 U.S.C. §§ 1391(c) and 1400(b).

COUNT FOR PATENT INFRINGEMENT

4. On June 18, 2002, the United States Patent and Trademark Office issued to Elan Patent No. 6,407,128 ("the '128 patent"), entitled "Method for Increasing the Bioavailability of Metaxalone." Since the date of issuance, Elan has been and remains the owner of the '128 patent. A copy of the '128 patent is attached hereto as Exhibit A.

5. Elan manufactures and markets metaxalone in the United States under the brand name Skelaxin®.

6. On information and belief, Eon filed an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA") pursuant to 21 U.S.C. § 355(j) to obtain approval for Eon to commercially manufacture, use and sell a generic equivalent of Elan's metaxalone product in the United States before the expiration of the '128 patent. The FDA assigned Eon's ANDA the number 40-445.

7. On information and belief, Eon also filed with the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that none of the claims of the '128 patent will be infringed by the manufacture, use or sale of Eon's generic metaxalone product and that all claims of the '128 patent are invalid.

8. On information and belief, on or after November 18, 2002, Elan received from Eon's Vice President of Business Development, Jeffrey Bauer, Ph.D., a letter purporting to be a Notice of Certification under 21 C.F.R. § 314.95, informing Elan of Eon's ANDA submission and corresponding certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV). A copy of this Notice is attached hereto as Exhibit B.

9. Under 35 U.S.C. § 271(e)(2)(A), Eon's submission to the FDA of ANDA No. 40-445 to obtain approval for the commercial manufacture, use or sale of its generic metaxalone product in the United States before the expiration of the '128 patent constituted infringement of the '128 patent.

10. On information and belief, the Eon generic metaxalone product will include labeling informing doctors and patients that administering the Eon generic metaxalone product with food will increase bioavailability.

11. On information and belief, pursuant to this labeling, the Eon generic metaxalone product will be administered to human patients with food to increase bioavailability, in a therapeutically effective amount for the treatment of musculoskeletal disorders.

12. On information and belief, Eon is aware that its generic metaxalone product with such labeling, which informs the public that taking metaxalone with food will increase

bioavailability, will actively induce, encourage, aid and abet patients and doctors in infringing the '128 patent.

WHEREFORE, Elan demands judgment as follows:

(a) finding that Eon has infringed one or more claims of the '128 patent;

(b) ordering pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval by the FDA of Eon's generic metaxalone product and Eon's ANDA No. 40-445 shall be no earlier than the date of expiration of the '128 patent;

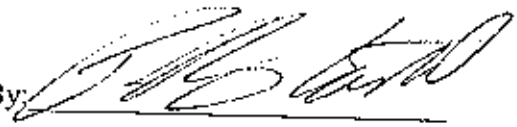
(c) granting injunctive relief pursuant to 35 U.S.C. § 271(e)(4)(B) against Eon, prohibiting the commercial manufacture, use, offer for sale, sale or importation of Eon's generic metaxalone product in the United States until the expiration of the '128 patent;

(d) directing Eon to amend its patent certification with respect to ANDA No. 40-445 from a Paragraph IV certification to a Paragraph III certification in accordance with 21 C.F.R. § 314.94(a)(12)(viii)(A); and

(e) awarding Elan attorney's fees pursuant to 35 U.S.C. § 285, costs of suit and any further and additional relief as this Court deems just and proper.

Dated: January 2, 2003
New York, New York

CAHILL GORDON & REINDEL

By: 

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(12) **United States Patent**
Scaife et al.

(10) **Patent No.: US 6,407,128 B1**
(45) **Date of Patent: Jun. 18, 2002**

(54) **METHOD FOR INCREASING THE BIOAVAILABILITY OF METAXALONE**

(75) Inventors: **Michael Scaife**, Poway; **Jaymin Shah**, Sunnyvale, both of CA (US)

(73) Assignee: **Elan Pharmaceuticals, Inc.**, South San Francisco, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/998,206**

(22) Filed: **Dec. 3, 2001**

(51) **Int. Cl.**[7] **A61K 31/42**
(52) **U.S. Cl.** **514/376**
(58) **Field of Search** 514/376

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,062,827	A	*	11/1962	Lunsford 260/307
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2001/0024659	A1		9/2001	Chen et al.

OTHER PUBLICATIONS

Monograph No. 5838 of the Merck Index (11th ed., 1989) for metaxalone.

Lunsford et al., 82 J. Am. Chem. Soc. 1166 (1960).

Skelaxin® monograph, 2001 Physicians' Desk Reference.

* cited by examiner

Primary Examiner—Raymond Henley, III
(74) *Attorney, Agent, or Firm*—Finnegan, Henderson, Farabow, Garrett & Dunner

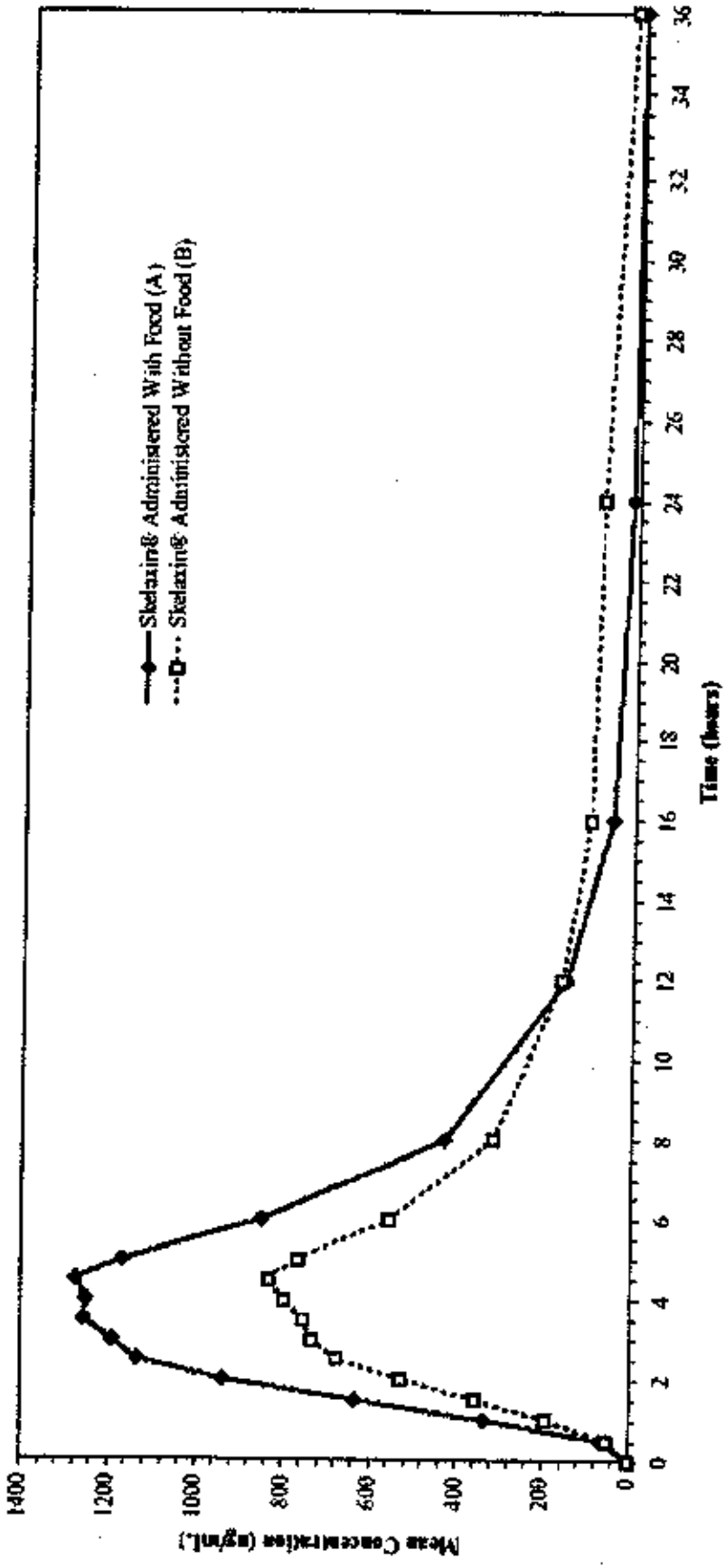
(57) **ABSTRACT**

A method of increasing the bioavailability of metaxalone by administration of an oral dosage form with food is provided, as well as an article of manufacture comprising an oral dosage form of metaxalone in a suitable container and associated with printed labeling which describes the increased bioavailability of the medication in the container when taken with food.

22 Claims, 1 Drawing Sheet

Figure I

Mean Plasma Concentration (0-36 hours)
Number =42



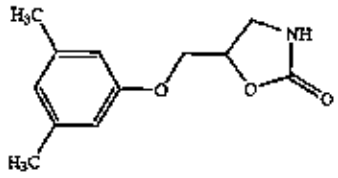
METHOD FOR INCREASING THE BIOAVAILABILITY OF METAXALONE

FIELD OF THE INVENTION

The invention relates to methods for increasing the bioavailability of a medicinal agent, namely metaxalone (5-[(3,5-dimethylphenoxy)methyl]-2 oxazolidinone).

BACKGROUND OF THE INVENTION

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



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

Skelaxin 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. The commercially available tablet contains: metaxalone, 400 mg along with inert compression tableting excipients.

Metaxalone is further described at Monograph no. 5838 of the Merck Index (Eleventh Addition, Merck & Co., 1989) and is also identified by CAS Registry Number: 1665-48-1. It is also known by the drug code, AHR-438; and the drug product containing it is marketed as Skelaxin® (a trademark of Elan Pharmaceuticals, Inc.).

Preparation of metaxalone is described in Lunsford et al., J. Am. Chem. Soc. 82, 1166 (1960) and U.S. Pat. No. 3,062,827 to Lunsford Nov. 6, 1962 Assignee A. H. Robins), which is incorporated herein in its entirety by reference. The '827 patent discloses the compound and related species as anticonvulsants and antispasmodics, however, these activities have not been borne out by clinical experience.

Metaxalone is a central nervous system depressant that has sedative and skeletal muscle relaxant effects. Metaxalone is indicated as an adjunct to rest, physical therapy and other measures for the relief of discomforts associated with acute, painful muscoloskeletal conditions. See Skelaxin® monograph, 2001 Physicians' Desk Reference®, Medical Economics Company, Inc. (publisher) Montvale, N.J.

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.

Pharmacokinetic studies have not previously been conducted to date to evaluate the effect of food on the pharmacokinetics of metaxalone. The hydrophobicity of the metaxalone molecule and the dosage amount required for a therapeutic effect both point to probably limited absorption from the gut when administered orally. More oral bioavailability of the drug substance has been sought to increase both speed of onset and amount of therapeutic effect.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plot of the mean plasma concentration of metaxalone in nanograms per milliliter versus the time elapsed from administration of the dosage form. Two (2) plots are shown for the 400 mg dosage form administered with and without food.

SUMMARY OF THE INVENTION

The subject of this invention is the unexpected finding that administration of metaxalone with food increases both the rate and extent of absorption via the oral dosage form in human subjects.

One aspect of this invention is a method of increasing the bioavailability of metaxalone in a human patient receiving metaxalone therapy wherein the metaxalone is contained in a pharmaceutical composition, which method comprises administering a therapeutically effective amount of metaxalone to the patient with food.

Another aspect of the invention is providing a method of increasing rate and extent of metaxalone absorption as measured by the drug concentration attained in the blood stream over time of a patient receiving, the drug in an oral dosage form which method comprises administering a therapeutically effective amount of metaxalone to the patient with food.

Preferably the therapeutic amount is between about 200 mg to about 900 mg, and more preferably between about 400 mg to about 800 mg. Unit dosage forms are preferred.

Preferably the food is a solid food with sufficient bulk and fat content that it is not rapidly dissolved and absorbed in the stomach. More preferably the food is a meal, such as breakfast, lunch or dinner. Advantageously the dosage is administered to the patient between about 30 minutes prior to about 2 hours after eating a meal, most advantageously the dosage is administered within 15 minutes of eating a meal. The terms "without food", "fasted" and "an empty stomach" are defined to mean the condition of not having consumed solid food for about 1 hour prior to until about 2 hours after such consumption.

Yet another aspect of this invention is providing information to prescribing physicians and patients receiving metaxalone therapy useful in maximizing the therapeutic effect of the oral dosage form, by recommending that metaxalone be taken within about half an hour of consuming food.

Another aspect of this invention is an article of manufacture that comprises a container containing a pharmaceutical composition comprising metaxalone wherein the container holds preferably the metaxalone composition in unit dosage form and is associated with printed labeling instructions advising of the differing absorption when the pharmaceutical composition is taken with and without food.

The effect of food on metaxalone absorption was identified in a study designed to compare the bioavailability of 400 mg of metaxalone in the formulation the drug product Skelaxin® administered to healthy volunteers with and without food.

An objective was to evaluate the bioavailability of metaxalone when administered to subjects with and without food. A single center, single dose, open-label, two-period, randomized, crossover trial in healthy subjects was conducted over a period of approximately 32 days.

The two study drug treatments were as follows:

Treatment A: metaxalone tablet (400 mg) administered with food

Treatment B: metaxalone tablet (400 mg) administered without food

In fed treatment condition A, study drug was taken 15 minutes after th e test meal. The test meal was consumed

over a 15 minute time period. There was a 6-day washout period between study drug administrations. Seventeen blood samples were collected, starting with baseline (0 hour) and at the following time points: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, and 36 hours.

A total of 44 subjects (31 males/13 females) were enrolled and dosed. Only the plasma of subjects who completed the study were assayed and used for the pharmacokinetic analysis.

A single center, single dose, open label, two-period crossover trial was devised for study in healthy subjects. Each administration was a single oral dose of one Skelaxin® 400 mg tablet with or without food. The study drug was administered as follows:

Treatment A: One (1) 400 mg tablet of metaxalone with 240 mL of room temperature water with food: Breakfast was given to the subjects 30 minutes prior to dosing and eaten within a 15 minute period. The dose of study drug was administered to the subjects 15 minutes after the breakfast was finished.

The breakfast consisted of the following:

2 eggs (fried in butter);
2 strips of bacon;
2 slices of toast with butter;
4 ounces of hash brown potatoes;
1 glass whole milk (8 ounces).

Treatment B: 1 tablet of metaxalone) with 240 mL of room temperature water without food. The study drug was administered with 240 mL room temperature water. A mouth check was performed to verify that the subjects swallowed the dose. Subjects were sequentially dosed at 1 minute intervals. The actual time of dosing was recorded on the Master Flow Sheet (refer to the Appendix 16.3.2 Clinical Study Data). Drug administration (1×400 mg capsule) was assisted with 240 mL of room temperature water consumed under direct observation. Immediately after administration of product, the subject's oral cavity was checked to confirm complete medication and fluid consumption. Dosing was completed as scheduled in 42 of 44 subjects.

The drug substance, metaxalone; was dosed in tablet form. Content: 400 mg; Route: Oral, Batch/Lot No.: SKLWW263F; Expiration Date: FEB03; Manufacturer: West-Ward Pharmaceutical Corp

All pharmacokinetic parameters were analyzed by noncompartmental methods. The following PK parameters were calculated for the two PK profiles and are defined as follows:

Tmax: Time to maximum concentration;

Cmax: Observed maximum concentration;

kel: Slope of terminal linear portion of concentration/time curve;

T½: Half-life of metaxalone calculated as: 0.693/Kel;

AUC(last): Area under the curve to last quantifiable concentration as measured by the trapezoidal rule;

AUC(inf): The AUC value extrapolated to infinity calculated as: AUC(inf)=AUC(last)+C(t)last/Kel where C(t) last is the last measurable concentration.

Statistical Analysis

All statistical analyses were performed using SAS® software version 6.08 or higher. The PK parameters between the two treatments were compared using an appropriate ANOVA model (analysis of variance) that includes term for treatment, sequence, and period effect. Ninety percent confidence interval was computed for the Cmax and AUC values of the fed treatment with fasting as the reference treatment. During the study there were no protocol deviations to confound the pharmacokinetic and bioavailability analyses. Study results were not corrected for drug potency. The individual test results are summarized in table I

TABLE I

Summary of AUC_{inf} and Ln-Transformed AUC_{inf} for Skelaxin ® Administered With Food (A) vs. Skelaxin ® Administered Without Food (B)

Subj	Seq.	A: With Food (ng/mL)	B: Without Food (ng/mL)	(A − B)	Ratio (A/B)	% Ratio (A/B) *100	Log_e A Ln(A)	Log_e B Ln(B)	Log_e Ratio Ln (Ratio)
2	1	9031	9855	824	0.916	91.64	9.108	9.196	0.087
3	2	9609	13103	3494	0.733	73.33	9.170	9.481	0.310
4	2	5011	3867	1144	1.296	129.58	8.519	8.260	0.259
5	1	3389	2530	859	1.340	133.95	8.128	7.836	0.292
6	2	10456	7302	3154	1.432	143.19	9.255	8.896	0.359
7	2	11217	11103	114	1.010	101.03	9.325	9.315	0.010
8	2	4025	3857	168	1.044	104.36	8.300	8.258	0.043
9	2	13708	8876	4832	1.544	154.44	9.526	9.091	0.435
11	2	8122	6570	1552	1.236	123.62	9.002	8.790	0.212
12	1	6739	5470	1269	1.232	123.20	8.816	8.607	0.209
13	2	4614	4360	254	1.058	105.83	8.437	8.380	0.057
14	1	17347	13467	3880	1.288	128.81	9.761	9.508	0.253
15	2	5488	3535	1953	1.552	155.25	8.610	8.170	0.440
16	1	12327	12025	302	1.025	102.51	9.420	9.395	0.025
17	1	4070	3320	750	1.226	122.59	8.311	8.108	0.204
18	1	5296	4365	931	1.213	121.33	8.575	8.381	0.193
19	2	8022	8271	249	0.970	96.99	8.990	9.021	0.031
20	2	2962	2874	88	1.031	103.06	7.994	7.963	0.030
21	1	9143	7173	1970	1.275	127.46	9.121	8.878	0.243
22	2	11873	7742	4131	1.534	153.36	9.382	8.954	0.428
23	1	10456	9983	473	1.047	104.74	9.255	9.209	0.046
24	1	6507	5529	978	1.177	117.69	8.781	8.618	0.163
25	2	12143	10272	1871	1.182	118.21	9.405	9.237	0.167
26	1	4519	5391	872	0.838	83.82	8.416	8.592	0.176

TABLE I-continued

Summary of AUC_{inf} and Ln-Transformed AUC_{inf} for Skelaxin ® Administered With Food (A) vs. Skelaxin ® Administered Without Food (B)

Subj	Seq.	A: With Food (ng/mL)	B: Without Food (ng/mL)	(A - B)	Ratio (A/B)	% Ratio (A/B) *100	Log_e A Ln(A)	Log_e B Ln(B)	Log_e Ratio Ln (Ratio)
27	1	5208	5061	147	1.029	102.90	8.558	8.529	0.029
28	2	5197	5012	185	1.037	103.69	8.556	8.520	0.036
29	1	10355	11601	1246	0.893	89.26	9.245	9.359	0.114
30	1	7350	6452	898	1.139	113.92	8.902	8.772	0.130
31	1	7899	7677	222	1.029	102.89	8.974	8.946	0.029
32	2	6719	4440	2279	1.513	151.33	8.813	8.398	0.414
33	2	11295	11316	21	0.998	99.81	9.332	9.334	0.002
34	2	13357	13580	223	0.984	98.36	9.500	9.516	0.017
35	2	10710	10138	572	1.056	105.64	9.279	9.224	0.055
36	1	19077	19329	252	0.987	98.70	9.856	9.869	0.013
37	1	6727	4454	2273	1.510	151.08	8.814	8.402	0.412
38	2	19024	9934	9090	1.915	191.50	9.853	9.204	0.650
39	1	3060	3284	224	0.932	93.18	8.026	8.097	0.071
40	1	5188	4203	985	1.234	123.44	8.554	8.344	0.211
41	1	7273	6574	699	1.106	110.63	8.892	8.791	0.101
42	2	3958	3642	316	1.087	108.68	8.283	8.200	0.083
43	1	8837	4642	4195	1.904	190.37	9.087	8.443	0.644
44	2	11427	11935	508	0.957	95.74	9.344	9.387	0.043

Differences were declared to be significant at the 5% level. The ratio of the geometric means for the in-transformed data and the corresponding 90% confidence intervals were calculated for AUC(last), AUC(inf), and Cmax. The calculations for the confidence intervals used the least squares means (LSMEANS) and the standard error of the estimate, both generated by the SAS® software.

The lower limit of quantitation for metaxalone was 10 ng/mL. For statistical analysis, subject sample values below the lower limit of quantitation were reported as zero.

Tables IIa and IIb summarize the results of the analyses performed on the pharmacokinetic parameters obtained from the fed and fasted states.

TABLE IIa

	Ln-Transformed	Ln-Transformed	Ln-Transformed
Metaxalone	AUC(last)	AUCinf	Cmax
Treatment A Geometric Mean	7525.00	7630.53	1536.23
Treatment B Geometric Mean	6094.12	6635.24	865.34
% Ratio	123.48	115.35	177.53
90% Confidence Interval	(116.40, 130.99)	(109.24, 121.80)	(156.62, 201.23)

TABLE IIb

Metaxalone	AUC(last)	AUCinf	Cmax	Tmax	T1/2
Treatment A Least Squares Mean	8439.62	8541.31	1773.61	4.29	2.37
Treatment B Least Squares Mean	6961.81	7478.90	983.37	3.32	9.04

With a 5% significance level, the ANOVA detected statistically significant differences between treatments for in-transformed AUC(last), AUCinf, and Cmax, as well as for untransformed AUC(last), AUC(inf), Cmax, Tmax, T½, and Kel. The ANOVA detected no statistically significant differences between periods or between sequences.

The mean $T_{1/2}$ (half-life) of metaxalone with food and without food were 2.37 and 9.04 hours respectively. The exact reason for this discrepancy is unclear. However, the AUC last is outside the confidence interval, indicating a significant food effect.

Ratio (A/B) of least-squares means for AUC(last), AUC (inf) and Cmax were 123.48%, 115.35% and 177.53%, respectively demonstrating that metaxalone administered with food increased both its rate and extent of absorption.

ANOVA detected statistically significant differences between treatments for ln-transformed AUC(last), AUC (inf), and Cmax, as well as for untransformed AUC(last), AUC(inf),Cmax, T½, and Kel. ANOVA did not detect any statistically significant differences between treatments for untransformed Tmax.

Conclusion: Administration with food increases both the rate and extent of absorption of metaxalone 400 mg tablets when administered as a single dose. The bioavailability of metaxalone 400 mg tablets increased when administrated with food.

Article of Manufacture

The article of manufacture comprises a container holding an immediate release pharmaceutical composition suitable for oral administration of metaxalone in combination with printed labeling instructions providing a discussion of when a particular dosage form should be administered with food and when it should be taken on an empty stomach. The composition will be contained in any suitable container capable of holding and dispensing the dosage form and which will not significantly interact with the composition and will further be in physical relation with the appropriate labeling advising that an immediate release tablet dosage form has less somnolence associated with its use if taken on an empty stomach and an immediate release multiparticulate dosage form has less somnolence associated with its use if taken with food. The labeling instructions will be consistent with the methods of treatment as described hereinbefore.

The labeling may be associated with the container by any means that maintain a physical proximity of the two, by way of non-limiting example, they may both be contained in a packaging material such as a box or plastic shrink wrap or may be associated with the instructions being bonded to the container such as with glue that does not obscure the labeling instructions or other bonding or holding means.

While the invention has been described by discussion of embodiments of the invention and non-limiting examples thereof, one of ordinary skill in the art may, upon reading the specification and claims, envision other embodiments and variations which are also within the intended scope of the invention and therefore the scope of the invention shall only be construed and defined by the scope of the appended claims.

We claim:

1. A method of increasing the oral bioavailability of metaxalone to a patient receiving metaxalone therapy comprising administering to the patient a therapeutically effective amount of metaxalone in a pharmaceutical composition with food.

2. The method of claim 1 wherein the therapeutically effective amount is 200 mg to 900 mg.

3. The method of claim 1 wherein the therapeutically effective amount is 400 mg to 800 mg.

4. The method of claim 1 wherein the administration to the patient occurs between 30 minutes prior to 2 hours after consuming food.

5. The method of claim 1 wherein the administration to the patient is substantially at the same time as the consumption of the food.

6. The method of claim 1 wherein the administration to the patient is immediately after the consumption of food up to 1 hour after said consumption.

7. The method of claim 1 wherein the pharmaceutical composition comprises a tablet.

8. The method of claim 7 wherein the tablet is in unit dosage form.

9. A method of increasing the rate and extent of absorption of an oral dosage form of metaxalone as measured by the drug concentration attained in the blood stream over time in a patient in need of a therapeutic effect thereof comprising, administering to the patient a therapeutically effective amount of metaxalone in a pharmaceutical composition with food.

10. The method of claim 9 wherein the therapeutically effective amount is about 200 mg to about 900 mg.

11. The method of claim 9 wherein the therapeutically effective amount is from about 400 mg to about 800 mg.

12. The method of claim 9 wherein the administration to the patient occurs between about 30 minutes prior to about 2 hours after consuming food.

13. The method of claim 9 wherein the administration to the patient is substantially at the same time as the consumption of the food.

14. The method of claim 9 wherein the administration to the patient is immediately after the consumption of food up to about one hour after said consumption.

15. The method of claim 9 wherein the pharmaceutical composition comprises a tablet.

16. The method of claim 15 wherein the pharmaceutical composition comprises a unit dosage form.

17. A method of increasing the oral bioavailability of metaxalone to a patient receiving metaxalone therapy comprising administering to the patient a pharmaceutical tablet comprising 400 mg to 800 mg of metaxalone, with food, wherein the administration results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food.

18. The method of claim 17 wherein the administration to the patient occurs between 30 minutes prior to 2 hours after consuming food.

19. The method of claim 17 wherein the administration to the patient is substantially at the same time as the consumption of the food.

20. The method of claim 17 wherein the administration to the patient is immediately after the consumption of food up to 1 hour after said consumption.

21. The method of claim 1, further comprising informing the patient that the administration of a therapeutically effective amount of metaxalone in a pharmaceutical composition with food results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food.

22. The method of claim 1, wherein the metaxalone is from a container with printed labeling advising that administration with food results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,407,128 B1
DATED : June 18, 2002
INVENTOR(S) : Scaife et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,
Line 38, before "Nov." insert open parenthesis -- (Nov. --;

Column 2,
Line 67, "th e" should read -- the --;

Column 5,
Line 29, "in-transformed" should read -- 1n-transformed --,
Line 66, "in-transformed" should read -- 1n-transformed --; and

Column 6,
Line 40, "In-transformed" should read -- 1n-transformed --.

Signed and Sealed this

Twenty-third Day of July, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

Eon Labs
The Pharmacy Drug Company

November 7, 2002

Dr. Garo Armen
Chairman of the Board
Elan Corporation, plc
Lincoln House, Lincoln Place
Dublin 2, Ireland

Re: Patent Certification Notice of SKELAXIN®

Dear Dr. Armen:

The purpose of this letter is to provide the notice and information required by Section 505(j)(2)(B)(I) and (II) of the Federal Food, Drug and Cosmetic Act.

Eon Labs, Inc. has filed an Abbreviated New Drug Application ("ANDA"), application number 40-445, with the Food and Drug Administration ("FDA") to obtain approval to engage in the commercial manufacture, use or sale and/or importation of a generic version of SKELAXIN® prior to the expiration of U.S. Patent 6,407,128 ("the '128 patent"). The '128 patent will expire December 3, 2021, according to the Orange Book.

A detailed statement of the factual and legal basis of Eon's opinion as to why its manufacture, use or sale and/or importation of the generic version of SKELAXIN® will not infringe any claim of the '128 patent is attached hereto and is incorporated as part of this letter. Additionally, the detailed statement will discuss why the claims of the '128 patent are invalid in view of the prior art.

Very truly yours,

Jeffrey Bauer, Ph.D.
Vice President of Business Development
Eon Labs, Inc.

Enc.

DETAILED STATEMENT PURSUANT TO 21 U.S.C. § 355(j)(2)(B)(ii) IN SUPPORT OF EON LABS MANUFACTURING, INC.'S PARAGRAPH IV PATENT CERTIFICATION

I. Introduction

Eon Labs, Inc. ("Eon") is an applicant for an Abbreviated New Drug Application ("ANDA") for metaxalone tablets. Pursuant to 21 U.S.C. § 355(j)(2)(B)(ii), Eon provides you with the following information:

Eon has submitted an ANDA for metaxalone tablets containing 400 mg of metaxalone per tablet and has identified Skelaxin® as the listed drug. The ANDA includes data from bioequivalence studies which establish that Eon's metaxalone tablets are bioequivalent to Skelaxin®. U.S. Patent 6,407,128 ("'128 patent") is listed in the FDA Orange Book as claiming the listed drug. Eon is hereby submitting a Patent Certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) to state that the '128 patent will not be infringed by the manufacture, use, offer for sale or sale of Eon's metaxalone tablets. In addition, it is our opinion that all of the claims of the '128 patent are invalid under 35 U.S.C. § 102(b) as anticipated by or under 35 U.S.C. § 103 as obvious in view of the prior art. The following detailed statement of the factual and legal bases for this assertion is hereby incorporated by reference into the notice to which it is appended.

II. Eon's Factual and Legal Bases

1. Background

A method of increasing the oral bioavailability of metaxalone is disclosed in the '128 patent, issued June 18, 2002 and assigned to Elan Pharmaceuticals, Inc. ("Elan"). The '128 patent will expire December 3, 2021. Metaxalone is indicated for the relief of discomforts associated with

expire December 3, 2021. Metaxalone is indicated for the relief of discomforts associated with acute, painful musculoskeletal conditions. The '128 patent teaches a method of increasing the oral bioavailability of metaxalone to a patient receiving metaxalone therapy comprising administering to the patient a therapeutically effective amount of metaxalone in a pharmaceutical composition with food. Metaxalone is the active ingredient in Skelaxin®.

2. The Invention Claimed in the '128 Patent

The '128 patent issued on June 18, 2002 from U.S. Patent Application Serial No. 09/998,206, filed December 3, 2001. The '128 patent will expire December 3, 2021 and is assigned to Elan Pharmaceuticals, Inc.

The '128 patent has 22 claims. Claims 1, 9, and 17 are in independent form. Claim 1 is directed to a method of increasing the oral bioavailability of metaxalone to a patient receiving metaxalone therapy comprising administering to the patient a therapeutically effective amount of metaxalone in a pharmaceutical composition with food. Claim 2 is the same method as claim 1 but is limited to a therapeutically effective amount of metaxalone of 200 mg to 900 mg. Claim 3 is the same method as claim 1 but is limited to a therapeutically effective amount of metaxalone of 400 mg to 900 mg. Claim 4 is the same method as claim 1 but is limited to administering to the patient a therapeutically effective amount of metaxalone between 30 minutes prior to 2 hours after consuming food. Claim 5 is the same method as claim 1 but where the administration of metaxalone to the patient is substantially at the same time as the consumption of the food. Claim 6 is the same method as claim 1 but where the administration of metaxalone to the patient is immediately after the consumption of food up to 1 hour after said consumption. Claim 7 is the

same method as claim 1 wherein the pharmaceutical composition comprises a tablet. Claim 8 further limits the tablet recited in claim 7 to a unit dosage form. Claim 9 is directed to a method of increasing the rate and extent of absorption of an oral dosage form of metaxalone as measured by the drug concentration attained in the blood stream over time in a patient in need of a therapeutic effect thereof comprising, administering to the patient a therapeutically effective amount of metaxalone in a pharmaceutical composition with food. Claim 10 is the same as the method of claim 9 wherein the therapeutically effective amount is about 200 mg to about 900 mg. Claim 11 is the same as the method of claim 9 wherein the therapeutically effective amount is from about 400 mg to about 800 mg. Claim 12 is the same as the method of claim 9 wherein the administration to the patient occurs between about 30 minutes prior to about 2 hours after consuming food. Claim 13 is the same as the method of claim 9 wherein the administration to the patient is substantially at the same time as the consumption of the food. Claim 14 is the same as the method of claim 9 wherein the administration to the patient is immediately after the consumption of food up to about one hour after said consumption. Claim 15 is the same as the method of claim 9 wherein the pharmaceutical composition comprises a tablet. Claim 16 is the same as the method of claim 15 wherein the pharmaceutical composition comprises a unit dosage form. Claim 17 is directed to a method of increasing the oral bioavailability of metaxalone to a patient receiving metaxalone therapy comprising administering to the patient a pharmaceutical tablet comprising 400 mg to 800 mg of metaxalone, with food, wherein the administration results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food. Claim 18 is the same as the method of claim 17 wherein the administration to the patient occurs between 30 minutes prior to 2 hours after consuming food. Claim 19 is the same as the method of claim 17 wherein the

administration to the patient is substantially at the same time as the consumption of the food. Claim 20 is the same as the method of claim 17 wherein the administration to the patient is immediately after the consumption of food up to 1 hour after said consumption. Claim 21 is the same as the method of claim 1, further comprising informing the patient that the administration of a therapeutically effective amount of metaxalone in a pharmaceutical composition with food results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food. Claim 22 is the same as the method of claim 1, wherein the metaxalone is from a container with printed labeling advising that administration with food results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food.

III. The Law

1. Claim Construction

A patent must include a specification, which comprises a written description sufficient to enable a person of ordinary skill in the art to make and use the invention. 35 U.S.C. § 112. The specification must "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention". *Id.* Like a deed to real property, the claims define the metes and bounds of the patent grant. *Corning Glass Works v. Sumitomo Elec. U.S.P., Inc.*, 868 F.2d 1251, 1257 (Fed. Cir. 1989).

The claims of a patent may be in independent form or dependent form. 35 U.S.C. § 112. An independent claim is a claim that does not refer to another claim. A dependent claim refers to

one or more other claims and is read as including all of the limitations recited in the dependent claim as well as all the limitations in each claim to which the dependent claim refers. 35 U.S.C. § 112; *Wahpeton Canvas Co., Inc. v. Frontier, Inc.*, 870 F. 2d 1546, 1553 (Fed. Cir. 1989).

Claim construction is a matter of law. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). " 'To ascertain the meaning of claims, we consider three sources: The claims, the specification and the prosecution history.' " *Markman, supra*, quoting, *Unique Concepts, Inc. v. Brown*, 939 F.2d 1558, 1561 (Fed. Cir. 1991). "Claims must be read in view of the specification of which they are a part," *Markman, supra*, citing, *Autogiro Co. of America v. United States*, 384 F.2d 391, 397 (Ct. Cl. 1967) and in view of the patent's prosecution history. *Markman*, 52 F.3d at 980, citing *Graham v. John Deere Co.*, 383 U.S. 1, 33 (1966). The claims are construed as one of ordinary skill in the art would have understood them at the time the invention was made. *Markman*, 52 F.3d at 979. "Words in a claim will be given their ordinary and accustomed meaning unless it appears that the inventor used them differently." *Envirotech v. Al George, Inc.*, 730 F.2d 753, 759 (Fed. Cir. 1984); *See, Intellicall, Inc. v. Phonometrics, Inc.*, 952 F.2d 1384, 1388 (Fed. Cir. 1992). "Claims must be interpreted and given the same meaning for purposes of both validity and infringement analyses." *Smithkline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 882 (Fed. Cir. 1988).

2. The Law of Anticipation

Under Section 35 U.S.C. §102(b) a patent is invalid if

> "the invention was patented or described in a printed publication in this or a foreign country ... more than one year prior to the date of the application for patent in the United States".

Where the invention claimed in a patent is described in a single publication that predates the filing of the U.S. patent application by more than one year, the claimed invention is said to be "anticipated" by the publication and hence invalid. When considering the validity of a patented invention, each claim of the patent must be considered separately, *i.e.*, each claim stands or falls on its own merits. 35 U.S.C. § 282.

"[A] claim is anticipated if each and every limitation is found either expressly or inherently in a single prior art reference." *Celeritas Technologies Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 1360 (Fed. Cir. 1998), *cert. denied*, 525 U.S. 1106 (1999), *citing Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 715 (Fed. Cir. 1984). To anticipate a claim and render it invalid, a prior art publication need not duplicate word for word what is in the claims. *Standard Havens Products, Inc. v. Gencor Industries, Inc.*, 953 F.2d 1360 (Fed. Cir. 1991), *cert. denied*, 506 U.S. 817 (1992). Furthermore, where "the result [recited in a claim] is a necessary consequence of what was deliberately intended, it is of no import that the [prior art] article's authors did not appreciate the results." *Mehl/Biophile International Corp. v. Milgraum*, 192 F.3d 1362, 1366 (Fed. Cir. 1999).

". . . [O]ne who seeks such a finding [of anticipation] must show that each element of the claim in issue is found, either expressly described or under principles of inherency, in a single prior art reference..."

* * *

"The law of anticipation does not require that the reference 'teach' what the subject patent teaches. Assuming that a reference is properly 'prior art,' it is only necessary that the claims under attack, as construed by the court, 'read on' something disclosed in the reference, i.e., all limitations of the claim are found in the reference, or 'fully met' by it."

Kalman v. Kimberly-Clark Corp., 713 F.2d 760, 771-772 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984).

3. The Law of Obviousness

Anticipation is not the sole basis for invalidating a patent claim. A claimed invention may also be invalid for obviousness if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103; see also *Graham v. John Deere Co.*, 383 U.S. 1,13. "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *In re Dow Chem.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

Where obviousness is based on a combination of two or more references, a finding of obviousness requires a showing of a suggestion, teaching, or motivation to combine the prior art references. *C.R. Bard, Inc. v. M3 Sys. Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998). This evidence may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. See *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996). This showing must be clear and particular, and broad conclusory statements about the teaching of multiple references, standing alone, are not "evidence." See *In re Dembiczak*, 175 F.3d 994, 1000 (Fed. Cir. 1999). However, the suggestion to combine need not be express and "may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1472 (Fed. Cir. 1997).

A determination of obviousness "does not require absolute predictability of success. ... [A]ll that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988); see also *In re Longi*, 759 F.2d 887, 897 (Fed. Cir. 1985). Neither does the determination require excluding routine experimentation. *In re Jones*, 162 USPQ 224, 226 (CCPA 1969) ("the selection of the preferred species would have been obvious to one skilled in the art particularly since the secondary proprieties were known or, if not known, could be determined by routine experimentation with a very limited number of species."); In *re Aller*, 105 USPQ2d 233, 235 (CCPA 1955) ("it is not inventive to discover the optimum or workable ranges by routine experimentation.")

4. Literal Infringement

To infringe a U.S. patent, the accused product or process must include each and every element recited in at least one claim of the patent. See, e.g. *Unique Concepts, Inc. v. Brown*, 939 F.2d 1558, 1562 (Fed. Cir. 1991).

If the accused embodiment falls squarely within the language of the claim, the infringement is said to be literal. But if an accused product or process lacks even a single claim element, that claim is not literally infringed. See, e.g. *Graver Tank and Manufacturing Co. v. Linde Air Products Co.*, 339 U.S. 605 (1950); *Pennwalt Corp. v. Durand-Wayland, Inc.*, 833 F.2d 931, 949 (Fed. Cir. 1987), *cert. denied*, 485 U.S. 961 (1988), and 485 U.S. 1009 (1988).

5. Infringement Under The Doctrine of Equivalents

The absence of literal infringement does not end the infringement analysis. Under the doctrine of equivalents a patent claim may be construed to cover an accused product or process outside the literal language of the claim. The doctrine of equivalents is applied on an element by element basis, not to the claim as a whole. Infringement under the doctrine of equivalents requires a determination that each element in the accused embodiment not encompassed by the literal claim language performs substantially the same function in substantially the same way to obtain substantially the same result as the corresponding element in the claim. *Dawn Equipment Co. v. Kentucky Farms Inc.*, 140 F.3d 1009, 1016 (Fed. Cir. 1998).

The Court of Appeals for the Federal Circuit has held that the foregoing tripartite test is part of a broader inquiry addressing the substantiality of the differences between the claim element(s) and

the allegedly equivalent element(s) in the accused embodiment. *See Hilton Davis Chemical Co. v. Warner-Jenkinson Company, Inc.*, 62 F.3d 1512, 1518 (Fed. Cir. 1995), *rev'd. on other grounds*, 520 U.S. 17 (1997). Thus, satisfaction of the tripartite test may not end the infringement inquiry, *Roton Barrier Inc. v. The Stanley Works*, 79 F.3d. 1112, 1126 (Fed. Cir. 1996), and all evidence in the record relevant to the substantiality of the differences must be considered. In assessing whether the differences are substantial, an important factor is whether persons of ordinary skill in the art would have known of the interchangeability of the element in the claim and the corresponding structure or step in the accused embodiment. See *Hilton Davis*, *62* F.3d at 1518-1519; *Graver*, 339 U.S. at 609. Evidence of copying or independent development is also relevant to infringement under the doctrine of equivalents, *Hilton Davis*, 62 F.3d. at 1519.

Under no circumstance does the doctrine of equivalents allow (1) the patentee to recapture claim coverage given up during prosecution in the Patent Office, or (2) the claims to be construed as covering that which is in the prior art. *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 870 (Fed. Cir. 1985).

6. Prosecution History Estoppel

The doctrine of equivalents is tempered by another judicial doctrine known as the doctrine of prosecution history estoppel. The prosecution history of a patent consists of the entire official record in the United States Patent and Trademark Office ("PTO"), including the specification with original claims, the official actions by the Examiner and the applicant's responses, including any amendments to the claims. Statements, admissions or representations made anywhere in the

prosecution history may give rise to an estoppel, barring the applicant from taking a different position in subsequent litigation. *Litton Systems, Inc. v. Honeywell, Inc.*, 140 F.3d 1449, 1458 (Fed. Cir. 1998).

In *Festo Corp. v. Shoketzu Kogyo Kabushiki Co., Ltd.*, 122 S.Ct. 1831, 62 U.S.P.Q. 2d 1701 (2002), the Supreme Court ruled that a claim limitation which has been narrowed during prosecution may still be entitled to a range of equivalents, but that those equivalents cannot include subject matter that was surrendered by the narrowing amendment. Thus, it is permissible to consider the proposed equivalent in weighing the scope of equivalents afforded by a narrowed limitation, *provided* that the proposed equivalent was not surrendered by the amendment. In other words, once the doctrine of prosecution history estoppel comes into play, the patentee can no longer rely upon a broad application of the doctrine of equivalents as to the particular claim limitation in question.

7. Direct Infringement

All of the claims of the '128 patent are method claims calling for the administration of a therapeutically effective amount of metaxalone to a patient receiving metaxalone therapy. The method as claimed would likely be carried out by doctors, other health care professionals and/or patients themselves and infringement by such persons is referred to as "direct" infringement. However, remedies for patent infringement are also available against defendants who "induce" others to directly infringe or who "contribute" to direct infringement by others.

8. Inducement of Infringement

35 U.S.C. § 271(b) provides that "whoever actively induces infringement of a patent shall be liable as an infringer." To succeed in a claim under 35 U.S.C. § 271(b), a plaintiff must show that the defendant had the "specific intent to encourage another's infringement." *Manville Sales Corp. v. Paramount Sys. Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990).

Circumstances which may lead to a finding of the required intent to induce infringement include giving a direct infringer instructions on how to use a patented process or designing a product to infringe. *Mendenhall v. Astec Industries Inc.*, 13 USPQ2d 1913 (E.D. Tenn. 1988), aff'd in unpublished opinion, 887 F.2d 1094 (Fed. Cir. 1989) ("To sustain a claim of inducement, the [the patent owner] must establish that [the accused infringer] purposefully caused, urged or encouraged another individual to infringe the ... patent with knowledge of the likely infringing result."); *Construction Prod. Corp. v. Hahn Builders, Inc.*, 573 F. Supp. 639 (E.D. Wis. 1983); *Goodwall Construction Co. v. Beers Construction Co.*, 216 USPQ 1006 (N.D. Ga. 1981) ("to sustain a claim of inducement, the plaintiff must establish that the defendant purposefully caused, urged or encouraged another individual to infringe plaintiff's patent with knowledge of the likely infringing result."); *National Tractor Pullers Ass'n, Inc. v. Watkins*, 205 USPQ 892, 913 (N.D. Ill. 1980); *Sims v. Mack Trucks, Inc.*, 459 F. Supp. 1198 (E.D. Pa. 1978), rev'd on other grounds, 608 F.2d 87, 203 USPQ 961 (3d Cir. 1979); ("such inducement requires acts which cause, urge, encourage or aid another to infringe and knowledge by the inducer that infringement is likely.").

9. Contributory Infringement

35 U.S.C. § 271(c) provides:

> Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

As is evident from the language of this statute, to be liable for contributory infringement the accused infringer must be selling a product which has no "substantial noninfringing use". *C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc.*, 911 F.2d 670 (Fed. Cir. 1998).

IV. Analysis

1. Claim Construction of Claims 1-22

As explained above, claims are interpreted based on three major sources: The claim language, the specification and the prosecution history.

The prosecution history indicates no substantive amendments to the pending claims that were finally allowed in the '128 patent. The Examiner did note, however, that recitation in certain of the pending method claims to labeling information (advising that the administration of

metaxalone with food results in an increase in bioavailability) is not subject matter covered under patent laws, or is a statement of intended use that does not constitute a limitation that can distinguish the claimed invention from the prior art.

From the foregoing, it is our opinion that when the claims are interpreted in light of the specification and the prosecution history, the claims must be construed as confined to a method for administering to a patient a therapeutically effective amount of metaxalone in a pharmaceutical composition with food.

2. The Manufacture And Sale Of a Generic Version of Skelaxin® Does Not Infringe Any Claims of the '128 Patent

An analysis of literal infringement requires a comparison of the properly construed claims with the accused conduct.

All of the claims of the '128 patent are so-called method of treatment claims, and each independent claims specifically requires the "administration" to the patient of a therapeutically effective amount of metaxalone. As we understand it, Eon will sell a generic drug product of Skelaxin® in the United States, but will not be responsible for oral administration of the product to patients[1]. Rather, independent health care professionals and the patients themselves will be responsible for oral administration of the product. That being the case, Eon could not be a direct infringer of the '128 patent.

[1] To the extent that Eon conducts clinical trials in the United States prerequisite to a ANDA filing for a generic drug product of Skelaxin®, such conduct would be exempt from any claim of patent infringement, at least to the extent such studies are conducted "solely for uses reasonably related to the development and submission of information" to the FDA. 35 U.S.C. § 271(e)(1).

It is our opinion that Eon is not liable for active inducement of infringement or contributory infringement. In response to a supplemental new drug application filed by Elan on October 16, 2001, the FDA has approved a new package labeling for Skelaxin® Tablets, 400 mg and 800 mg, which incorporates a Pharmacokinetics section comparing the mean peak plasma concentrations and the extent of absorption of metaxalone under fasted and fed patient conditions. Presumably, Eon will also be required by the FDA to have the same Pharmacokinetics section. The section notes that the clinical relevance is unknown for the observed differences in the mean peak plasma concentrations and the extent of absorption of metaxalone under fasted and fed patient conditions. Further, the Dosage and Administration section of the package labeling is silent as to whether Skelaxin® Tablets should be taken with or without food. Thus, Eon's use of the same language as in Elan's new package labeling for Skelaxin® Tablets would not constitute active inducement of infringement or contributory infringement of any claims of the '128 patent as there is no active solicitation or instructions by Eon to administer metaxalone with food. Thus, claim 1 is not infringed under 35 U.S.C. § 271(b). Since claim 1 is not infringed, claims 2-22 are also not infringed. See *Wolverine World Wide Inc. v. Nike Inc.*, 32 USPQ2d 1338, 1342 (Fed. Cir. 1994), quoting *Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553, 10 USPQ2d 1201, 1208 (Fed. Cir. 1989) ("It is axiomatic that dependent claims cannot be found infringed unless the claims from which they depend have been found to have been infringed").

Eon's generic drug product of Skelaxin® will be sold as a drug that is capable of substantial noninfringing uses, e.g. oral administration of the drug without food. Thus, the generic drug product lacks one of the elements required for contributory infringement. At least for this

reason, the sale of the generic drug product does not constitute contributory infringement of claims 1-22 of the '128 patent.

3. All the Claims Of The '128 Patent Are Invalid In View Of Prior Art.

As noted above, pursuant to 35 U.S.C. § 102(b), a patent claim is invalid if the claimed subject matter was "patented or described in a printed publication in this or a foreign country ... more than one year prior to the date of the application for patent in the United States".

In an article published August 11, 1995 by Micromedex, Inc., it is disclosed that a number of skeletal muscle relaxants, including metaxalone, "may be crushed and mixed with a little food or liquid if needed to make the tablets easier to swallow." See Exhibit 1 ("Micromedex reference").

In an article entitled "Musculoskeletal Disorders and Their Management with a New Relaxant published April 1965 by K. Fathie in Clinical Medicine, it is stated that "Metaxalone was well accepted and except for mild nausea in six cases, was apparently well tolerated. Nausea might have been less prominent if the medication had been taken with food." See Exhibit 2 ("Fathie reference").

Both of the above references were published more than one year prior to the filing of the application for the '128 patent (December 3, 2001), and are proper prior art references to the '128 patent. It is our opinion that each of the above references renders all of the claims of the '128 patent invalid. While the below discussion refers to the Micromedex reference, the invalidity arguments applies equally as well to the Fathie reference.

Claim 1 of the '128 patent reads:

> "A method of increasing the oral bioavailability of metaxalone to a patient receiving metaxalone therapy comprising administering to the patient a therapeutically effective amount of metaxalone in a pharmaceutical composition with food."

The Micromedex reference teaches the oral administration of metaxalone with food. The Micromedex reference does not teach that the oral bioavailability of metaxalone to a patient increases when metaxalone is taken with food. However, the oral administration of metaxalone with food inherently possesses this characteristic, i.e., it increases the oral bioavailability of metaxalone. Because this characteristic is inherent to the method, it is inherently taught in the Micromedex reference. Consequently, all of the limitations of claim 1 are taught by the Micromedex reference, either explicitly or under the principles of inherency. Accordingly, the Micromedex reference anticipates claim 1 and for at least this reason it is our opinion that claim 1 is invalid.

In addition, claims 2-22 are invalid for the following reasons.

The Micromedex reference further teaches that metaxalone should be administered to adults and teenagers at a dosage of 800 mg three to four times a day. Claims 2 and 3, which are dependent on claim 1, recite amounts of metaxalone to be administered with food that encompass 800 mg. Accordingly, the Micromedex reference anticipates claims 2 and 3.

The Micromedex reference teaches that metaxalone should be administered with food. Claims 4 and 5, which are dependent on claim 1, recite that metaxalone is to be administered with food within a time period that encompasses administering to the patient metaxalone substantially at the same time as the consumption of food. Accordingly, the Micromedex reference anticipates claims 4 and 5.

Claim 6 is dependent on claim 1 and recites that the administration of metaxalone to the patient be done immediately after the consumption of food up to 1 hour after said consumption. The Micromedex reference teaches that metaxalone should be administered with food. This reference would make obvious the administration of metaxalone to a patient immediately after the consumption of food. Accordingly, claim 6 is invalid as obvious in view of the Micromedex reference.

Claims 7 and 8 are dependent on claim 1 and recite that the metaxalone is in a tablet form and in a unit dosage form, respectively. The Micromedex reference discloses that a crushed tablet or tablets having a total metaxalone of 800 mg should be administered with food. Accordingly, the Micromedex reference anticipates claims 7 and 8.

Independent claim 9 is directed to a method of increasing the rate and extent of absorption of an oral dosage form of metaxalone as measured by the drug concentration attained in the blood stream over time in a patient in need of a therapeutic effect thereof comprising, administering to the patient a therapeutically effective amount of metaxalone in a pharmaceutical composition

with food. The Micromedex reference teaches the oral administration of metaxalone with food. The Micromedex reference does not teach increasing the rate and extent of absorption of an oral dosage form of metaxalone as measured by the drug concentration attained in the blood stream over time in a patient when metaxalone is taken with food. However, the oral administration of metaxalone with food inherently possesses this characteristic, i.e., it increases the rate and extent of absorption of an oral dosage form of metaxalone as measured by the drug concentration attained in the blood stream over time in a patient. Because this characteristic is inherent to the method, it is inherently taught in the Micromedex reference. Consequently, all of the limitations of claim 9 are taught by the Micromedex reference, either explicitly or under the principles of inherency. Accordingly, the Micromedex reference anticipates claim 9 and for at least this reason it is our opinion that claim 9 is invalid.

Claims 10-16 are dependent on claim 9 and recite additional limitations identical to those recited in claims 2-8. Claims 10-16 are invalid for the same reasons as claims 2-8 are invalid.

Claim 17 is directed to a method of increasing the oral bioavailability of metaxalone to a patient receiving metaxalone therapy comprising administering to the patient a pharmaceutical tablet comprising 400 mg to 800 mg of metaxalone, with food, wherein the administration results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food. The Micromedex reference teaches the oral administration of metaxalone with food. The Micromedex reference does not teach increasing the oral bioavailability of metaxalone wherein the administration results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of

metaxalone compared to administration without food when metaxalone is taken with food. However, the oral administration of metaxalone with food inherently possesses this characteristic, i.e., it increases the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food. Because this characteristic is inherent to the method, it is inherently taught in the Micromedex reference. Consequently, all of the limitations of claim 17 are taught by the Micromedex reference, either explicitly or under the principles of inherency. Accordingly, the Micromedex reference anticipates claim 17 and for at least this reason it is our opinion that claim 17 is invalid.

Claims 18-20 are dependent on claim 17 and recite additional limitations identical to those recited in claims 4-6. Claims 18-20 are invalid for the same reasons as claims 4-6 are invalid.

Claim 21 is dependent on claim 1 and has the further step of informing the patient that the administration of a therapeutically effective amount of metaxalone in a pharmaceutical composition with food results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food. Claim 22 is dependent on claim 1 and has the limitation that the metaxalone is from a container with printed labeling advising that administration with food results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food. In the prosecution history of the '128 patent, the Examiner noted that "[i]n the pharmaceutical art, it is routine, if not required, to include a package insert containing instructions for the use of the packaged pharmaceutical. The specific printed information is not material covered under patent laws, but rather copyright laws. Also, even if

such were covered under patent laws, the limitation in the claim relating to the instructions would be seen as a statement of intended use for the claimed composition which does not impart any physical limitation to the composition that is not found in, or made obvious by the prior art." Accordingly, the specific language or information conveyed to the patient regarding the pharmacokinetics of metaxalone required by claims 21 and 22, is not required to be disclosed by the prior art reference for it to anticipate the claims. Rather, as long as the prior art reference teaches the oral administration of metaxalone with food, and such administration inherently leads to the pharmacokinetics of metaxalone stated in claims 21 and 22, then the reference anticipates these claims. This is indeed what the Micromedex reference teaches and inherently leads to.

V. Conclusion

For at least the reasons discussed above, it is our opinion that the making, using, offering for sale, selling or importing into the United States of a generic drug product of Skelaxin® with the same package labeling language as used for Skelaxin® does not infringe any claim of the '128 patent. In addition, it is our opinion that claims 1-22 of the '128 patent are invalid as anticipated or rendered obvious in view of either the Micromedex or Pathie reference.

Exhibit 1.

Micromedex Article

Skeletal Muscle Relaxants (Systemic)

Contents of this page:

Brand Names

Soma commonly used brand names are:

In the U.S.—

- Carbacot[5]
- EZE-DS[3]
- Maolate[2]
- Paraflex[3]
- Parafon Forte DSC[3]
- Relaxazone[3]
- Remular[3]
- Remular-S[3]
- Robaxin[5]
- Robaxin-750[5]
- Skelaxin[4]
- Skelex[5]
- Soma[1]
- Strifon Forte DSC[3]
- Venadom[1]

In Canada—

- Robaxin[5]
- Robaxin-750[5]
- Soma[1]

Note:	For quick reference, the following skeletal muscle relaxants are numbered to match the corresponding brand names.

This information applies to the following medicines:

1. Carisoprodol (kar ais oh proe doh'l)
4. Metaxalone (me TAX a lone)

2. Chlorphenesin (klor-FEN-e-sin)†
3. Chlorzoxazone (klor-ZOX-e-zone)‡†
5. Methocarbamol (meth-oh-KAR-ba-mole)‡

‡ Generic name product may be available in the U.S.

§ Generic name product may be available in Canada

▪ Not commercially available in the U.S.

† Not commercially available in Canada

Category

- **Skeletal muscle relaxant** —Carisoprodol; Chlorphenesin ; Chlorzoxazone; Metaxalone; Methocarbamol

Description

Skeletal muscle relaxants are used to relax certain muscles in your body and relieve the stiffness, pain, and discomfort caused by strains, sprains, or other injury to your muscles. However, these medicines do not take the place of rest, exercise or physical therapy, or other treatment that your doctor may recommend for your medical problem. Methocarbamol also has been used to relieve some of the muscle problems caused by tetanus.

Skeletal muscle relaxants act in the central nervous system (CNS) to produce their muscle relaxant effects. Their actions in the CNS may also produce some of their side effects.

In the U.S., these medicines are available only with your doctor's prescription. In Canada, some of these medicines are available without a prescription.

These medicines are available in the following dosage forms:

Oral

- Carisoprodol
  - Tablets (U.S. and Canada)
- Chlorphenesin
  - Tablets (U.S.)
- Chlorzoxazone
  - Tablets (U.S.)
- Metaxalone
  - Tablets (U.S.)
- Methocarbamol
  - Tablets (U.S. and Canada)

Parenteral

- Methocarbamol
  - Injection (U.S. and Canada)

Before Using This Medicine

In deciding to use a medicine, the risks of taking the medicine must be weighed against the good it will do. This is a decision you and your doctor will make. For the skeletal muscle relaxants, the following should be considered:

Allergies—Tell your doctor if you have ever had any unusual or allergic reaction to any of the skeletal muscle relaxants or to carbromal, mebutamate, meprobamate (e.g., Equanil), or tybamate. Also tell your health care professional if you are allergic to any other substances, such as foods, preservatives, or dyes.

Pregnancy—Although skeletal muscle relaxants have not been shown to cause birth defects or other problems, studies on birth defects have not been done in pregnant women. Studies in animals with metaxalone have not shown that it causes birth defects.

Breast-feeding—Carisoprodol passes into the breast milk and may cause drowsiness or stomach upset in nursing babies. It is not known whether chlorphenesin, chlorzoxazone, metaxalone, or methocarbamol passes into the breast milk. However, these medicines have not been reported to cause problems in nursing babies.

Children—Studies with the skeletal muscle relaxants have been done only in adult patients, and there is no specific information comparing use of these medicines in children with use in other age groups. However, carisoprodol and chlorzoxazone have been used in children. They have not been reported to cause different side effects or problems in children than they do in adults.

Older adults—Many medicines have not been tested in older people. Therefore, it may not be known whether they work exactly the same way they do in younger adults or if they cause different side effects or problems in older people. There is no specific information about the use of skeletal muscle relaxants in the elderly.

Other medicines—Although certain medicines should not be used together at all, in other cases two different medicines may be used together even if an interaction might occur. In these cases, your doctor may want to change the dose, or other precautions may be necessary. When you are taking a skeletal muscle relaxant, it is especially important that your health care professional know if you are taking any of the following:

- Alcohol or
- Central nervous system (CNS) depressants or
- Tricyclic antidepressants (amitriptyline [e.g., Elavil], amoxapine [e.g., Asendin], clomipramine [e.g., Anafranil], desipramine [e.g., Pertofrane], doxepin [e.g., Sinequan], imipramine [e.g., Tofranil], nortriptyline [e.g., Aventyl], protriptyline [e.g., Vivactil], trimipramine [e.g., Surmontil])—The chance of side effects may be increased

Other medical problems—The presence of other medical problems may affect the use of a skeletal muscle relaxant. Make sure you tell your doctor if you have any other medical problems, especially:

- Allergies, history of, or
- Blood disease caused by an allergy or reaction to any other medicine, history of, or
- Drug abuse or dependence, or history of, or
- Kidney disease or
- Liver disease or
- Porphyria—Depending on which of the skeletal muscle relaxants you take, the chance of side effects may be increased; your doctor can choose a muscle relaxant that is less likely to cause problems

- Epilepsy—Convulsions may be more likely to occur if methocarbamol is given by injection

Proper Use of This Medicine

Chlorzoxazone, metaxalone, or methocarbamol tablets may be crushed and mixed with a little food or liquid if needed to make the tablets easier to swallow.

Dosing—

The dose of these medicines will be different for different patients. *Follow your doctor's orders or the directions on the label.* The following information includes only the average doses of these medicines. *If your dose is different, do not change it* unless your doctor tells you to do so.

For carisoprodol
- For *oral* dosage form (tablets):
  - For relaxing stiff, sore muscles:
    - Adults and teenagers—350 milligrams (mg) four times a day.
    - Children up to 5 years of age—Dose must be determined by your doctor.
    - Children 5 to 12 years of age—6.25 mg per kilogram (2.5 mg per pound) of body weight four times a day.

For chlorphenesin
- For *oral* dosage form (tablets):
  - For relaxing stiff, sore muscles:
    - Adults and teenagers—800 milligrams (mg) three times a day, at first. Your doctor may decrease your dose after you begin to feel better.
    - Children—Use and dose must be determined by your doctor.

For chlorzoxazone
- For *oral* dosage form (tablets):
  - For relaxing stiff, sore muscles:
    - Adults and teenagers—500 milligrams (mg) three or four times a day.
    - Children—125 to 500 mg three or four times a day, depending on the child's size and weight.

For metaxalone
- For *oral* dosage form (tablets):

- For relaxing stiff, sore muscles:
  - Adults and teenagers—800 milligrams (mg) three or four times a day.
  - Children—Use and dose must be determined by your doctor.

For methocarbamol

- For *oral* dosage form (tablets):
  - For relaxing stiff, sore muscles:
    - Adults and teenagers—1500 milligrams (mg) four times a day, at first. Your doctor may decrease your dose after you begin to feel better.
    - Children—Use and dose must be determined by your doctor.
- For *injection* dosage form:
  - For relaxing stiff, sore muscles:
    - Adults and teenagers—1 to 3 grams a day, injected into a muscle or a vein. This total daily dose may be divided into smaller amounts that are given several times a day, especially when the medicine is injected into a muscle.
    - Children—Use and dose must be determined by your doctor.

Missed dose—

If you miss a dose of this medicine and remember within an hour or so of the missed dose, take it right away. But if you do not remember until later, skip the missed dose and go back to your regular dosing schedule. Do not double doses.

Storage—

To store this medicine:

- Keep out of the reach of children.
- Store away from heat and direct light.
- Do not store this medicine in the bathroom, near the kitchen sink, or in other damp places. Heat or moisture may cause the medicine to break down.
- Do not keep outdated medicine or medicine no longer needed. Be sure that any discarded medicine is out of the reach of children.

Precautions While Using This Medicine

If you will be taking this medicine for a long time (for example, more than a few weeks), your doctor should check your progress at regular visits.

This medicine will add to the effects of alcohol and other CNS depressants (medicines that slow down the nervous system, possibly causing drowsiness). Some examples of CNS depressants are antihistamines or medicine for hay fever, other allergies, or colds; sedatives, tranquilizers, or sleeping medicine; prescription pain medicine or narcotics; barbiturates; medicine for seizures; other muscle relaxants; or anesthetics, including some dental anesthetics. *Do not drink alcoholic beverages, and check with your doctor before taking any of the medicines listed above, while you are using this medicine.*

Skeletal muscle relaxants may cause blurred vision or clumsiness or unsteadiness in some people. They may also cause some people to feel drowsy, dizzy, lightheaded, faint, or less

alert than they are normally. *Make sure you know how you react to this medicine before you drive, use machines, or do anything else that could be dangerous if you are dizzy or are not alert, well-coordinated, and able to see well.*

For *diabetic patients*:

- Metaxalone (e.g., Skelaxin) may cause false test results with one type of test for sugar in your urine. If your urine sugar test shows an unusually large amount of sugar, or if you have any questions about this, check with your health care professional. This is especially important if your diabetes is not well controlled.

Side Effects of This Medicine

Along with its needed effects, a medicine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention.

Check with your doctor as soon as possible if any of the following side effects occur:

Less common

Fainting; fast heartbeat; fever; hive-like swellings (large) on face, eyelids, mouth, lips, and/or tongue; mental depression; shortness of breath, troubled breathing, tightness in chest, and/or wheezing; skin rash, hives, itching, or redness; slow heartbeat (methocarbamol injection only); stinging or burning of eyes; stuffy nose and red or bloodshot eyes

Rare

Blood in urine; bloody or black, tarry stools; convulsions (seizures) (methocarbamol injection only); cough or hoarseness; fast or irregular breathing; lower back or side pain ; muscle cramps or pain (not present before treatment or more painful than before treatment); painful or difficult urination; pain, tenderness, heat, redness, or swelling over a blood vessel (vein) in arm or leg (methocarbamol injection only); pinpoint red spots on skin; puffiness or swelling of the eyelids or around the eyes; sores, ulcers, or white spots on lips or in mouth; sore throat and fever with or without chills; swollen and/or painful glands; unusual bruising or bleeding ; unusual tiredness or weakness; vomiting of blood or material that looks like coffee grounds; yellow eyes or skin

Other side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. However, check with your doctor if any of the following side effects continue or are bothersome:

More common

Blurred or double vision or any change in vision; dizziness or lightheadedness; drowsiness

Less common or rare

Abdominal or stomach cramps or pain; clumsiness or unsteadiness; confusion; constipation; diarrhea; excitement, nervousness, restlessness, or irritability; flushing or redness of face; headache ; heartburn; hiccups; muscle weakness;

nausea or vomiting ; pain or peeling of skin at place of injection (methocarbamol only); trembling; trouble in sleeping; uncontrolled movements of eyes (methocarbamol injection only)

Although not all of the side effects listed above have been reported for all of these medicines, they have been reported for at least one of them. However, since all of these skeletal muscle relaxants have similar effects, it is possible that any of the above side effects may occur with any of these medicines.

In addition to the other side effects listed above, chlorzoxazone may cause your urine to turn orange or reddish purple. Methocarbamol may cause your urine to turn black, brown, or green. This effect is harmless and will go away when you stop taking the medicine. However, if you have any questions about this, check with your doctor.

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

Revised: 08/11/1995

Exhibit 2.

Musculoskeletal Disorders and Their Management with a New Relaxant

The American Academy of Neurological and Orthopaedic Surgeons

Musculoskeletal Disorders and Their Management with a New Relaxant

KAZEM FATHIE, M.D., F.A.C.S., F.I.C.S., Ph.D.

Metaxalone was administered to 50 patients with skeletal muscle disorders, of whom 42 were available for followup. A beneficial therapeutic effect was observed in 80 per cent of those with low back pain and stiffness indicative of muscle spasm of the back, hip and leg muscles. Ten patients had mild side effects.-A This report is based on a clinical evaluation of a skeletal muscle relaxant with a chemical structure unrelated to that of other skeletal muscle relaxants. This compound, metaxalone,t is 5- (3,5-dirnethylphenoxymethyl) - 2-oxazolidinone(1). It is a tasteless, odorless, white crystalline powder that melts without decomposition at 121.5 to 123 C. Extensive pharmaeodynamic studies(2) showed metaxalone to have a specific antagonism to strychnine-induced convulsions. It completely blocked the polysynaptic linguomandiibular and flexor reflexes at closes that did not alter the normal posture and gait of unanesthetizecl animals. It had neither sedative nor tranquilizer properties, but was analgetic. No apparent effects on blood pressure, heart rate, body temperature, electrocardiogram or electromyogram were noted. Thus, any muscle relaxant effect from this drug observed clinical- ly is probably due to an interruption of noxious impulses at the internuncial neurons of the cord.

Materials and Methods

The present study included 50 patients treated on an outpatient basis at the Medical College of Virginia. The conditions inclucled low back pain and stiffness, acute lumbosacral pain, cervical stiffness or torticohis, arthritic pain and parkinsonism. The type of discomfort and degree approximated those usually observed in a general medical clinic.

A complete interview and medical examination was performed on each patient and laboratory studies were ordered. These included a complete blood count, urinalysis, and blood urea nitrogen. The degree of muscle stiffness and skeletal muscle spasm was assessed by interview, inspection, palpation and estimation of the range of motion. Muscle spasm was identified as sudden, violent, involuntary contractions of a muscle or muscle group attended by pain and interference with proper function. Patients ranged in age from 20 to 80 years with the largest number in the sixth decade. The duration of symptoms ranged from one day to 30 years with a median duration

of approximately two years. Dosage ranged from 2400 to 4000 mg. daily (average 3200 mg.) and duration of treatment from one to 21 days with an average of 14 days.

Results

Of the 50 patients originally included in the study, completed records are available on 42 and eight did not return for re- evaluation. Of the 42, results were considered excellent in 16, good in seven, fair in six and poor in 13. These results are shown by diagnosis in Table 1.

Table 1

Results of Metaxalone Therapy in 42 Patients

Diagnosis	No. of Patients	Therapeutic Effects*			
		1	2	3	4
A. Low back pain and stiffness	19	9 (47%)	2 (11%)	5 (26%)	3 (16%)
B. Low back pain, stiffness of back and hips	8	3 (37%)	4 (50%)	5 (26%)	3 (16%)
C. Low back and leg pain	8	4 (50%)	—	1 (13%)	3 (37%)
SUBTOTAL	35	(46%)	(17%)	(17%)	(20%)
D. Arthritis	5		1		4
E. Parkinsonism	2				2
TOTAL	42	16	7	6	13

* 1= Excellent; 2 = good; 3 = fair; 4 = poor

The greatest therapeutic effect was obtained in patients with painful spasm or stiffness of the back and leg muscles. When groups A, B, and C in Table 1 are taken as a whole, 80% had a positive therapeutic response to medication. Only one of the five arthritic patients had a favorable re- sponse and there was no improvement in the symptomatology of parkinsonism in two patients. It was interesting to observe complete control of hemiballismus in one of the latter patients. The other com- plained of an increase in rigidity after one day's medication and because of this and his emotional status the medication was discontinued. Two of the patients (C) with low back and leg pain failed to respond to medication in the clinic and were subsequently treated surgically for herniated disc by the neurosurgical service. The third was a 200-pound patient with tendencies toward malingering.

Case Histories

Case I

A woman of 35, weight 153 pounds, was admitted with symptoms of low back pain and stiffness present intermittently for approximately six months. Physical examination revealed no neurological deficit or changes in reflexes. There was no evidence of disc pathology. Her blood pressure was 120/80, pulse 88. The history was non-contributory. Metaxalone was prescribed, 800 mg. three times daily. On re-examination five days later, the patient reported that pain was gone and stiffness diminished. The patient was well satisfied with the results of therapy. Medication was continued for an additional four days. When re-examined eight days after initial admission, all muscle stiffness and pain were resolved, and results were confirmed by re-examination two weeks later. Hemoglobin, white blood count and differential, urinalysis, and blood urea nitrogen were within normal limits. There were no side effects.

Case II

A man of 59, weight 155 pounds, had for several years a history of muscle tightness in the cervical area. Approximately one week prior to admission the patient noticed pain and stiffness of the right hip and lumbosacral area. Blood pressure on admission was 160/100, pulse 90. The neurological examination was negative. Metaxalone was prescribed, 800 mg. three times daily for four days. On re-examination, neck and back muscles were more relaxed and spasticity was completely absent. Patient reported moderate residual pain. Dosage was increased to 800 mg. four times daily. Within two days, only mild pain and stiffness remained and within two weeks after the original visit, all symptoms had disappeared. This patient mentioned polyuria on the first night after initiation of drug therapy, but no other untoward symptoms thereafter. Hemoglobin, white blood count, differential, urinalysis and blood urea nitrogen remained un- changed.

CASE III

The patient was admitted with symptoms of acute back and leg pain and acute rigidity of lumbar muscles of three to four days' duration. On admission blood pressure was 110/80, pulse 90. History revealed symptoms of arthritis for two to three years. Neurological examination was negative except for diminished deep tendon reflexes and some radiation of pain to both hips. Metaxalone was prescribed, 800 mg. four times daily for 14 days. On re-examination after seven days, pain was completely re-solved and only minor muscle spasm was detectable on palpation. Fourteen days after admission patient felt much improved, pain and stiffness gone.

Side Effects

Of the 42 patients, 32 were without side effects that could be attributed to the medication. Six patients mentioned a feeling of nausea during the period of drug therapy. Of these, two had slight

nausea and loss of appe- tite on the first day or two of treatment. The nausea then disappeared and medication was continued for 10 to 14 days. Two patients had nausea on days 13 and 14 and one patient had to discontinue medication during the second week of treatment because of persistent nausea. The sixth patient with gastrointestinal symptoms developed fever and pain (possible arach- noiditis from myelograph dye) after taking only 10 tablets and was transferred to another service. In contrast, two other patients noticed an increase in appetite during drug therapy. One of these patients, a 106-pound woman with chronic painful rigidity of the lower back had previously complained of poor appetite and was very pleased with the unexplained improvement. Two patients, one of whom had an excellent therapeutic effect, complained of slight headache. One patient mentioned polyuria on the first day of drug treatment and another mentioned frequent micturition. One patient reported a loss of taste while taking metaxalone.

Comments

This study was conducted during the early clinical trials of metaxalone when the indications were not definitely pinpointed. It was recognized at that time that the drug had marked skeletal muscle relaxant properties in animals, but the clinical efficacy and indications had not been determined. Hence, no effort was made to limit the study population to patients with a specific syndrome or condition with common etiology. In some patients, the muscle manifestations were more prominent and, in others, muscle involvement appeared to be secondary to joint pain. In all, there was stiffness, limited range of motion and guarding. Neurologic examination in most cases was negative. The onset of drug action appeare to be quite rapid. Painful symptoms began to subside after the second or third dose and, in those cases in which the patient was to respond favorably, a definite therapeutic response was observed in three days. Medication was continued in most cases for 10 to 14 days unless the patient was uncooperative or side effects intervened.

The problems inherent in evaluating a new therapeutic agent in a clinic population markedly reduce the amount of valid data on which to base conclusions of efficacy and patient acceptability. Many of the patients were repeaters whose attendance at the clinic was sporadic and who did not return for followup examination. Although it may be presumed that symptoms were sufficiently alleviated to permit reasonable comfort or a return to normal activity, this has not been confirmed. Sufficient experience was gained with the drug, however, to arrive at certain impressions of its therapeutic usefulness and primary indications. Metaxalone was well accepted and except for mild nausea in six cases, was apparently well tolerated. Nausea might have been less prominent if the medication had been taken with food. Other untoward symptoms that occurred during the period of drug

therapy could not be un- equivocally attributed to drug action. Metaxalone was most useful in those patients in whom acute spasm and muscle stiffness were most prominent. In cases of arthritic pain or neurological involvement such as parkinsonism, no beneficial effect could be discerned. A dose of 800 mg. four times a day appeared to be optimum. A moderate therapeutic effect was observed in some patients who were started on 2400 mg. daily and as much as 4000 mg. was tolerated. For general use, 3200 mg. a day appears appropriate.

Summary and Conclusions

1. A skeletal muscle relaxant, metaxalone, was dispensed to 50 patients with skeletal muscle disorders, treated on an outpatient basis at the Medical College of Virginia. Sufficient followup data were available on 42 of these patients to permit evaluation of drug effect.
2. A beneficial therapeutic effect was observed in 80% of the patients with low back pain and stiffness indicative of muscle spasm of the back, hip and leg muscles. The drug was not effective in the two patients with parkinsonism or in four out of five patients with arthritis. One arthritic patient noticed a reduction in muscle spasm

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