

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-901

STATISTICAL REVIEW(S)

STATISTICAL/CLINICAL REVIEW AND EVALUATION.

NDA#: 20-901
Applicant: Galderma
Name of Drug: Metro lotion (metronidazole topical lotion, 0.75%)
Documents Reviewed: Volumes 1.1, 1.7, 1.12-1.17, dated December 2, 1998
Type of Report: NDA review
Indication: Treatment of rosacea
Medical officer: Phyllis Huene, M.D. (HFD-540)

Introduction.

Metronidazole topical lotion, 0.75%, is a line extension to marketed drugs MetroGel and MetroCream. The sponsor submitted a report of one pivotal trial, Protocol No. CR.U9418. The objective of this clinical trial is to demonstrate the safety and efficacy of metronidazole lotion (metrolotion), applied BID for 12 weeks in patients with moderate to severe rosacea.

MATERIALS AND METHODS

Study Design

This randomized, double-blind, vehicle-controlled study in patients with moderate to severe rosacea compares metrolotion to its vehicle. A total of 144 patients from six independent study centers were enrolled (24 patients per center). Following establishment of eligibility criteria, each patient was randomized to receive either metronidazole lotion or vehicle and instructed to apply the study medication twice daily to the entire facial area for twelve weeks. Patients were evaluated at Baseline and at Weeks 3, 6, 9, and 12.

Patient population consisted of 144 patients of any gender and race, over 18 years of age who were diagnosed with moderate to severe rosacea in accordance with the following criteria:

- Presence of at least 6 but no more than 50 total papules and/or pustules;
- Presence of moderate to severe erythema;
- Presence of telangiectasia.

Efficacy and Safety Evaluations

Primary efficacy endpoints were change in inflammatory lesion counts and the Investigator's Global Assessment of improvement in rosacea.

Investigator's Global Assessment of Improvement

The Global Assessment of improvement as compared to Baseline was recorded as a summary of reduction in inflammatory lesion counts and erythema. The Investigators used Baseline photographs to assist them with each follow-up Global Assessment. The Investigator assessed the patient's overall improvement or response to treatment at each follow-up visit according to the following six-point scale:

- Worse** Exacerbation of either erythema or quantitative assessment of papules and/or pustules.
- No change** Condition remains the same.
- Minimal Improvement** Slight improvement in the quantitative assessment of papules and/or pustules, and/or slight improvement in erythema.
- Definite Improvement** More pronounced improvement in the quantitative assessment of papules and/or pustules, and/or more pronounced improvement in erythema.
- Marked Improvement** Obvious improvement in the quantitative assessment of papules and/or pustules, and/or obvious improvement in erythema.
- Clear** No papules or pustules and minimal residual erythema.

Success in Investigator's Global Assessment was defined as Investigator's assessment of Definite Improvement, Marked Improvement or Clear.

Safety Evaluations

All patients received a cutaneous evaluation of the treated area at each visit consisting of subjective assessments of stinging/burning, pruritus, and dryness. These parameters were assessed to determine the Baseline irritation associated with rosacea as well as irritation caused by the study medication. These parameters were evaluated on a four-point ranking scale (none, mild, moderate, or severe).

Statistical Methods

This was a randomized, double-blind, multicenter, vehicle-controlled, parallel study. Within each center, patients were assigned to one of the two treatments using a randomization procedure by blocks of six.

Primary Efficacy Variables used by the Statistical Reviewer are:

- 1) Percent change from baseline in Inflammatory Lesion count and
- 2) Success rate in Investigator's Global Assessment of Improvement . Success was defined as Investigator's Global Assessment of Definite/Marked Improvement or Clear.

The primary efficacy timepoint was called Endpoint and was equal to the time of the last evaluation conducted for a given patient (usually Week 12).

Efficacy Populations

Evaluable (Per protocol) population was the primary efficacy population and the Intent-to-treat (ITT) was the secondary efficacy population. ITT analysis included all data for all patients enrolled in the study. The following criteria were used to exclude patients from the Evaluable population:

- Patients with a visit window greater than 7 days.
- Patients dropping out before the Week 3 visit.
- Patients missing more than five consecutive days of dosing.
- Patients missing 2 or more consecutive visits before Week 12.
- Patients receiving concomitant medications were excluded on a case-by-case basis depending on the number of days of the interfering or contraindicated therapy.

Statistical Analyses

The primary efficacy variable, "categorized" percent reduction from Baseline, was tested using Cochran-Mantel-Haenszel (CMH) test. The riddit transformation was used and the Investigator formed the strata. Analysis of the actual lesion count was also performed to support the results for the percent change in lesion count. The actual lesion counts were analyzed by ANCOVA. The model included treatment, Investigator, treatment-by-Investigator interaction and baseline lesion count. A square root transformation was used to meet the assumptions of homogeneity of variance and normality. The least square means were transformed back to the original units by squaring each mean .

A dichotomized Global Assessment (success rate in Global Assessment) was another primary

efficacy variable. All-category analysis of the Global Assessment was also performed to support the results for the dichotomized Global Assessment. All-category Global Assessment, dichotomized Global Assessment, and skin safety variables were compared between treatment groups at each time period using the CMH test.

RESULTS

One hundred forty-four patients were enrolled in the study. The treatment distribution was 72 patients assigned to metronidazole lotion and 72 patients assigned to vehicle. Each of the six centers enrolled 24 patients (12 patients in each treatment group). Of the 144 patients enrolled, 125 (65 on metronidazole lotion and 60 on vehicle) completed the entire twelve-week study as planned ($p=0.22$).

All 144 patients were dosed at least one time and were considered evaluable for safety analysis and included in the ITT analyses. Forty-two patients (18 on metronidazole lotion and 24 on vehicle) deviated slightly from the protocol and were considered nonevaluable and excluded from the primary efficacy analyses ($p=0.27$).

Patient and Disease Characteristics

The gender distribution was as follows: 37 (26%) males and 107 (74%) females. Patients were divided within treatment groups as follows: 16 (22%) males and 56 (78%) females on metronidazole lotion; 21 (29%) males and 51 (71%) females on vehicle. There was no statistically significant difference between treatment groups relative to gender distribution ($p = 0.45$).

The majority of the patients enrolled were white. There was no statistically significant difference between treatment groups relative to race distribution ($p = 1.00$).

The mean age in years for the treatment groups was similar, 48 for the metronidazole lotion group and 47 for the vehicle group. Patients ranged in age from 23 to 81 for the metronidazole lotion group and from 22 to 76 for the vehicle group. There was no statistically significant difference between treatment groups relative to age ($p = 0.59$).

At Baseline, each patient was categorized according to skin type: oily, normal or dry. There was no statistically significant difference between treatment groups relative to skin type ($p = 0.22$).

To qualify for enrollment, all patients were required to have either moderate or severe rosacea. The majority of patients enrolled were evaluated as having moderate rosacea (80.6% in the metronidazole lotion group and 81.9% in the vehicle group). There was no statistically significant difference between treatment groups with regard to rosacea severity ($p = 0.83$). At Baseline, the specific area of rosacea involvement was noted on the case report form: nose,

cheek(s), forehead, and/or chin. There was no statistically significant difference between treatment groups relative to the areas of rosacea involvement at Baseline ($p = 1.00$).

Efficacy Evaluations

The primary efficacy analysis was conducted for the two primary efficacy variables (percent change in Inflammatory lesion count and Global Assessment) at Endpoint using the Evaluable population. The ITT analysis was a secondary efficacy analysis. The results in the Evaluable and ITT populations were similar.

Inflammatory Lesion Count

At Baseline, mean lesion counts were similar for both treatment groups ($p = 0.70$). Mean lesion counts were reduced by both treatments at all follow-up visits. There was significantly fewer inflammatory lesions in the metronidazole group at all follow-up visits (beginning at Week 6, $p < 0.001$). Beginning at Week 6, Baseline lesions were reduced from 15.8 to 8.1 for patients receiving metronidazole lotion and resulted in a mean lesion count of 6.8 at Endpoint. Baseline lesion counts reduced from 16.1 to 11.8 at Endpoint for vehicle-treated patients. There were consistently fewer inflammatory lesions for metronidazole-treated patients at all visits for each Investigator.

Table 1 presents the results for the primary efficacy variable, the percent change in inflammatory lesion counts, in the Evaluable population. At all visits, metronidazole lotion was statistically significantly more effective ($p < 0.001$) than vehicle relative to the percent change of inflammatory lesion count. Similar results were shown in the ITT analysis ($p < 0.001$).

Table 1: Mean Percent Change in Inflammatory Lesion Counts (Evaluable population)			
	Metronidazole Lotion (N=66 at endpoint)	Vehicle (N=62 at endpoint)	p-value
Week 6	-44.2	-17.5	<0.001
Week 9	-55.2	-25.8	<0.001
Week 12	-55.4	-21.9	<0.001
Endpoint	-52.1	-22.4	<0.001

Sub-group analyses for inflammatory lesion counts and percent reduction was performed by demographic categories. When grouped according to gender, a consistent effect on inflammatory lesion reduction was shown in the metronidazole group at all timepoints for both males and females. When analyzed according to age groups (20-39, 40-59, and 60-89), a trend favoring metronidazole lotion was demonstrated in all three age groups. A skin-type analyses (oily, normal, or dry) indicates a similar consistent effect shown by metronidazole lotion on lesion reduction at all timepoints except Week 3 when patients with oily skin on vehicle showed more reduction in lesions than did the metronidazole lotion group. When grouped by disease severity (moderate or severe), patients randomized to the metronidazole lotion group experienced a consistent reduction in inflammatory lesions as compared to patients receiving vehicle.

Global Assessment of Improvement

The Investigator's Global Assessment of improvement was analyzed both as a categorical variable and a dichotomized variable (comparison of success rates). In the all-category analysis of the Investigator's Global Assessment of rosacea improvement, metronidazole lotion was significantly more effective ($p < 0.001$ beginning from Week 6) than vehicle. For all Investigators combined at Endpoint, 65.2% metronidazole lotion patients showed a definite/marked improvement or a complete clearing of rosacea as compared to 33.9% of patients on vehicle. Table 2 summarizes results of the dichotomized analysis. Similar results were obtained in the ITT analysis ($p < 0.001$).

Table 2: Success Rates (Percent of Patients with Definite Improvement, Marked Improvement, or Clear) for Investigator's Global Assessment of Improvement (Evaluable population)			
	Metronidazole Lotion (N=66 at endpoint)	Vehicle (N=62 at endpoint)	p value in CMH test
Week 6	49.1%	20.7%	<0.001
Week 9	66.1%	38.9%	<0.001
Week 12	71.4%	40.8%	<0.001
Endpoint	65.2%	33.9%	<0.001

In both the primary efficacy and ITT analyses, patients receiving metronidazole lotion showed a statistically significant improvement in their rosacea condition as compared to vehicle when analyzed according to demographic and disease characteristic subgroups.

Safety

Safety evaluation parameters were analyzed for all 144 patients enrolled. There was no treatment difference at Baseline with regard to dryness scores ($p = 0.67$). Both treatments similarly reduced the symptom of dryness with no statistically significant differences shown ($p > 0.16$). At Endpoint, over 91% of patients in both treatments had no or mild dryness.

No statistically significant treatment differences were found at any timepoint relative to stinging/burning ($p > 0.11$). The majority of patients in both treatment groups reported absent or mild stinging/burning at Baseline (82% in the metronidazole group and 83.3% in the vehicle group). The percentage of patients with absent or mild stinging/burning increased throughout the study resulting in more than 93% of patients in both treatment groups with absent or mild stinging/burning at Endpoint.

Results for pruritus were similar to those reported for stinging/burning. Both treatments reduced the symptom of pruritus throughout the study with no statistically significant differences between treatments ($p > 0.21$). The Baseline percentage of patients reporting absent or mild pruritus was approximately 75% for both treatments. This increased during the study resulting in 93% of patients in both treatment groups reporting absent or mild pruritus at Endpoint.

Adverse Events and discontinuation due to Adverse Events.

A total of 84 patients reported 194 medical events: 42 (58%) patients reported 103 events in the metronidazole lotion group and 42 (58%) of patients reported 91 events in the vehicle group. Tables 3 shows number of patients reporting adverse events related to therapy in two treatment groups.

Adverse Event	Metronidazole Lotion , N (%)	Vehicle, N (%)	P-value
Allergic reaction	2 (2.8%)	0	0.5
Contact dermatitis	2 (2.8%)	0	0.5
Erythema	4 (5.6%)	0	0.12
Rosacea Worsening	1 (1.4%)	4 (5.6%)	0.37
Discontinuation due to AE related to therapy	4 (5.6%)	7 (9.7%)	0.53

REVIEWER'S CONCLUSIONS (which may be conveyed to the sponsor):

Metro lotion is a line extension to the currently marketed MetroGel and MetroCream. The sponsor submitted results of one well controlled Phase III study to support the claim of safety and efficacy of Metro lotion in the treatment of moderate to severe rosacea. The primary efficacy variables are percent change from baseline in Inflammatory Lesion count and success rate in Investigator's Global Assessment of Improvement. Success is defined as Investigator's Global Assessment of Definite/Marked Improvement or Clear. The primary efficacy population is the Evaluable (Per Protocol) population and the primary efficacy timepoint is the time of the last evaluation conducted for a given patient (usually Week 12).

The efficacy results of the study show that, metronidazole lotion is statistically significantly better than vehicle ($p < 0.001$) relative to both primary efficacy variables, percent change from baseline in the Inflammatory Lesion Count and success rate in the Investigator's Global Assessment of Improvement. The analysis of the mean lesion counts and the all-category analysis of the Investigator's Global Assessment of Improvement support these results. Results in the ITT population are very similar to the results in the Evaluable population ($p < 0.001$). The subgroup analysis by age, gender, and skin type indicates a consistent effect of metro lotion as shown by inflammatory lesion count and Investigator's Assessment of Improvement.

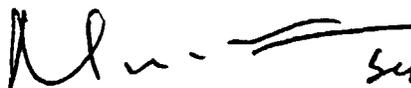
The safety analysis found no statistically significant differences between metro lotion and vehicle groups at any timepoint relative to stinging/burning, pruritus, allergic reactions, contact dermatitis, erythema, rosacea worsening, and dry skin ($p > 0.12$).

Overall, the results of the pivotal study CR.U9418 statistically support the sponsor's claim that metro lotion (metronidazole topical lotion 0.75%) is safe and effective in the treatment of moderate to severe rosacea.

151

08.28.98

Valeria Freidlin, Ph.D.
Mathematical Statistician, Biometrics IV

 *Sept 9, 98*

Concur: Rajagopalan Srinivasan, Ph.D.
Team Leader, Biometrics IV

cc:

Archival NDA 20-901

HFD-540

HFD-540/Mrs. Wright

HFD-540/Dr. Wilkin

HFD-540/Dr. Huene

HFD-725/Dr. Huque

HFD-725/Dr. Srinivasan

HFD-725/Dr. Freidlin

HFD-344/Dr. Carreras

Chron. (HFD-725)

This review contains 9 pages.

wordfile\metrolot\20901_1.r1\08-28-98

STATISTICAL/CLINICAL REVIEW AND EVALUATION.**ADDENDUM**

OCT 28 1998

NDA#: 20-901

Applicant: Galderma

Name of Drug: Metro lotion (metronidazole topical lotion, 0.75%)

Documents Reviewed: Revised Draft Labeling Amendment dated 10.6.1998

Type of Report: NDA review

Indication: Treatment of rosacea

Medical officer: Phyllis Huene, M.D. (HFD-540)

Introduction.

The sponsor submitted the Revised Draft Labeling Amendment and proposed to use **median** percent change in inflammatory lesion count instead of the **mean** percent change as was planned in the original protocol.

Reviewer's Comment:

According to the Protocol, **mean** inflammatory lesion count was the primary efficacy variable. The primary efficacy analysis was analysis of covariance. Analysis of covariance uses means, not medians. As a supporting analysis, the Protocol stated the CMH row means score statistic. The use of median was never stated in the Protocol.

According to the ICH Guideline, Section E9, the primary efficacy variable and the proposed statistical analysis should be clearly specified in the protocol before the trial begins. Redefinition of the primary efficacy variable and primary statistical analysis after unblinding will be unacceptable, since the biases introduced are difficult to assess.

According to Revised Draft Labeling Amendment, outliers made the MetroLotion group distribution skewed and therefore, medians should be used instead of the means. As can be seen from the data, both MetroLotion and Vehicle group have one outlier. Presence of outlier in the active group cannot be used as a reason for redefining the primary efficacy variable and

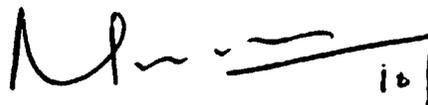
statistical method. Therefore, this reviewer recommends using the mean percent change in inflammatory lesion count as was stated in the original protocol and in the original draft labeling. Therefore, the first row in the label table should be:

Inflammatory lesion counts	55%	20%	P<0.001
----------------------------	-----	-----	---------

|S|

10.28.98

Valeria Freidlin, Ph.D.
Mathematical Statistician, Biometrics IV


10/28/98

Concur: Rajagopalan Srinivasan, Ph.D.
Team Leader, Biometrics IV

cc:

Archival NDA 20-901

HFD-540

HFD-540/Mrs. Wright

HFD-540/Dr. Wilkin

HFD-540/Dr. Huene

HFD-725/Dr. Huque

HFD-725/Dr. Srinivasan

HFD-725/Dr. Freidlin

HFD-344/Dr. Carreras

Chron. (HFD-725)

This addendum contains 2 pages.

wordfile\metrolot\addendum\10-28-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-901

MICROBIOLOGY REVIEW(S)

JUN - 3 1998

REVIEW FOR DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS, HFD-540
OFFICE OF NEW DRUG CHEMISTRY, MICROBIOLOGY STAFF, HFD-805
MICROBIOLOGISTS'S REVIEW NO. 1

May 29, 1998

MICROBIOLOGY REVIEWER: Carol K. Vincent

- A. 1. NDA No.: 20-901
DRUG PRODUCT NAME: MetroLotion™ [metronidazole topical lotion]
Topical Lotion, 0.75%
APPLICANT: Galderma Laboratories, Inc.
P. O. Box 331329
Fort Worth, Texas 76163
Manufacturer: DPT Laboratories, Ltd.
307 E. Josephine Street
San Antonio, Texas 78215
2. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Non-sterile, topical lotion.
3. METHOD(s) OF STERILIZATION:
Not applicable, non-sterile, topical dosage form with preservative.
4. PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION:
The anti-protozoal and anti-bacterial drug product is intended for treatment of inflammatory papules and pustules of rosacea.
5. DRUG PRIORITY CLASSIFICATION: 3 S

- B. 1. DOCUMENT DATE: November 28, 1997
2. DOCUMENT RECEIVED FOR REVIEW: December 22, 1997
3. AMENDMENT: February 12, 1998
4. AMENDMENT RECEIVED FOR REVIEW: February 20, 1998
5. RELATED DOCUMENTS:

NDA 19-737 Galderma Laboratories, Inc. MetroGel (metronidazole topical gel) Topical Gel, 0.75%
NDA 20-531 Galderma Laboratories, Inc. MetroCream (metronidazole topical cream) Topical Cream, 0.75%

C. REMARKS: This NDA is the third dosage form of this drug substance from the same applicant.

D. CONCLUSION and RECOMMENDATION:

Galderma Laboratories, Inc.'s NDA 20-901 for MetroLotion™ [metronidazole topical lotion] Topical Lotion, 0.75% is not recommend for approval from the microbiology perspective.

CC:
Orig. NDA 20-901
HFD-160/Consult/CK Vincent [HFD-805]
HFD-540/Higgins/DeCamp/
Drafted by: CK Vincent/01-30-98/
Revised by: CK Vincent/05-15-98/05-29-98

151
Carol K. Vincent
Review Microbiologist [HFD-805] 5-29-98
PAC 6/3/98
Filename: NDA20901

HFD-540 Wristed

SEP 24 1998

Review for Division of Dermatologic and Dental Drug Products, HFD-540
Office of New Drug Chemistry, Microbiology Staff, HFD-805
Microbiologists's Review No. 2

September 24, 1998

MICROBIOLOGY REVIEWER: Carol K. Vincent

- A. 1. **NDA No.:** 20-901
DRUG PRODUCT NAME: MetroLotion™ [metronidazole topical lotion]
Topical Lotion, 0.75%
APPLICANT: Galderma Laboratories, Inc.
P. O. Box 331329
Fort Worth, Texas 76163
Manufacturer: DPT Laboratories, Ltd.
307 E. Josephine Street
San Antonio, Texas 78215
- 2. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:**
Non-sterile, topical lotion.
- 3. **METHOD(S) OF STERILIZATION:**
Not applicable, non-sterile, topical dosage form with preservative.
- 4. **PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION:**
The anti-protozoal and anti-bacterial drug product is intended for treatment of inflammatory papules and pustules of rosacea.
- 5. **DRUG PRIORITY CLASSIFICATION:** 3 S

- B. 1. **AMENDMENT DATE:** August 21, 1998
- 2. **DOCUMENT RECEIVED FOR REVIEW:** September 3, 1998
- 3. **AMENDMENT (fax copy):** September 14, 1998
- 4. **AMENDMENT RECEIVED FOR REVIEW:** September 14, 1998
- 5. **RELATED DOCUMENTS:**

NDA 19-737	Galderma Laboratories, Inc.	MetroGel (metronidazole topical gel) Topical Gel, 0.75%
NDA 20-531	Galderma Laboratories, Inc.	MetroCream (metronidazole topical cream) Topical Cream, 0.75%

C. **REMARKS:** This NDA is the third dosage form of this drug substance from the same applicant.

D. **CONCLUSION and RECOMMENDATION:**

We recommend approval for Galderma Laboratories, Inc.'s NDA 20-901, MetroLotion™ [metronidazole topical lotion] Topical Lotion, 0.75% is from the microbiology perspective.

CC:
Orig. NDA 20-901
HFD-160/Consult/CK Vincent [HFD-805]
HFD-540/Higgins/DeCamp/
Drafted by: CK Vincent/09-23-98/

IS! 3-24-98

Carol K. Vincent
Review Microbiologist [HFD-805]
CK 9/24/98

Attachment: 09-14-98 memorandum of conversation
Filename:NDA20901.2nd

HFD-540

OCT 28 1998

REVIEW FOR HFD-540
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF NDA 20-901 BI
28 October 1998

A. 1. NDA 20-901 BI

APPLICANT: Galderma Laboratories, Inc.
P.O. Box 331329
Fort Worth, TX 76163-1329

2. PRODUCT NAMES: MetroLotion™ (metronidazole topical lotion)
Topical Lotion, 0.75%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a topical formulation.

4. METHODS OF STERILIZATION:
The product is not a sterile product but, is subject to microbial limits specifications.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is indicated for use in treatment of metronidazole responsive dermatological conditions.

B. 1. DATE OF INITIAL SUBMISSION: 2 December 1997

2. DATE OF AMENDMENT: 14 September 1998 (Subject of this Review)

3. RELATED DOCUMENTS: (none)

4. ASSIGNED FOR REVIEW: 28 October 1998

REMARKS: The amendment is a formal submission of the change in specification for the finished drug product Microbial Limit Test. The change consists of separate specifications for total aerobic microbial count (Not More Than CFU/g) and total molds and yeasts count (Not More Than CFU/g) and the absence of *Pseudomonas aeruginosa* and

Galderma, NDA 20-901 BI, MetroLotion™ Topical Lotion, 0.75%, Microbiologist's Review

Staphylococcus aureus. This change was previously discussed with Dr. Peter Cooney, Supervisory Microbiologist.

D. CONCLUSIONS: The application is recommended for approval on the basis of microbial quality of the drug product. ✓

PS

28 October 1998

Paul Stinavage, Ph.D. ✓

File 10/28/98

cc: Original NDA 20-901
HFD-540/Div. Files/M. Wright
HFD-805/Consult File/Stinavage/C. Vincent

Drafted by: P. Stinavage, 28 October 1998
R/D initialed by P. Cooney

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-901

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

MAY 8 1995

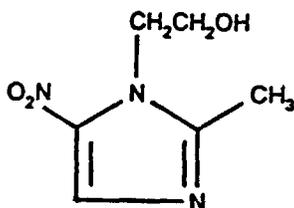
Clinical Pharmacology/Biopharmaceutics Review

NDA:	20-901	SUBMISSION DATE:	12/2/97
PRODUCT:	Metronidazole Topical Lotion, 0.75% MetroLotion™		
SPONSOR:	Galderma Laboratories, Inc. Fort Worth, TX 76163	REVIEWER:	Veneeta Tandon, Ph.D.

Review of NDA**I. Background**

MetroLotion™ Topical Lotion, 0.75% is the third form of metronidazole to be sponsored by Galderma laboratories. NDAs for MetroGel® Topical Gel, 0.75% and MetroCream® Topical cream, 0.75% were approved on November 22, 1988 and September 20, 1995, respectively. All three dosage forms are indicated for twice daily (morning and night) application in the topical treatment of rosacea. Development of the lotion dosage form was initiated by the sponsor for preference in patients with dry skin, who would prefer an easily spreadable lotion formulation.

Metronidazole is a member of the imidazole class of anti-bacterial agents and is classified therapeutically as an anti-protozoal and anti-bacterial agent. Chemically, metronidazole is 2-methyl-5-nitro-1H-imidazole-1-ethanol.



Rosacea is a chronic disorder of unknown etiology characterized by recurrent episodes of inflammatory papules and pustules, facial erythema, and telangiectasia. The mechanism of action of metronidazole in treating rosacea is not known; however, it is postulated to be related to its inhibitory effect on inflammatory neutrophil cell function.

II. Recommendation

The in-vivo pharmacokinetic study in healthy subjects and the in-vitro liberation and penetration studies provide an understanding to the systemic availability and percutaneous absorption of metronidazole from the lotion formulation in comparison to the marketed MetroGel® formulation and supports a recommendation for the approval of this NDA from the pharmacokinetics standpoint. The sponsor is also committed to conduct a pharmacokinetic study in patients as well. Labeling recommendations for the "Pharmacokinetics" section of the label should be conveyed to the sponsor.

Index

I. Background	*	*	*	*	*	*	*	*	1
II. Recommendation		*	*	*	*	*	*	*	1
III. Formulation	*	*	*	*	*	*	*	*	2
IV. Analytical Validation		*	*	*	*	*	*	*	3
V. Pharmacokinetic studies overview			*	*	*	*	*	*	4
A. In-vivo studies									
a. Single dose comparison in healthy volunteers			*	*	*	*	*	*	4
B. In-vitro studies									
b. Comparison of in-vitro liberation-penetration from two lotion formulations and gel formulation in human skin		*	*	*	*	*	*	*	12
b. Comparison of in-vitro liberation-penetration from two formulations across full human thickness skin		*	*	*	*	*	*	*	11
VI. Conclusions	*	*	*	*	*	*	*	*	14
VII. Appendix *	*	*	*	*	*	*	*	*	15

III. Formulation

MetroLotion™ is an oil-in-water emulsion containing 0.75% (w/w) metronidazole. The following is the qualitative and quantitative composition of the proposed commercial formulation for Metronidazole Topical Lotion, 0.75%

Ingredient	Per gram	percent (w/w)
✓Metronidazole, USP	7.5 mg	0.75
✓Carbomer 941, NF	mg	
✓Glycerine, USP	mg	
✓Polyethylene Glycol, 400, NF	mg	
✓Benzyl Alcohol, NF	mg	
✓Steareth-21*	mg	
✓Glyceryl Stearate (and) PEG-100 Stearate*	mg	
✓Stearyl Alcohol, NF	mg	
✓Light Mineral Oil, NF	mg	
✓Cyclomethicone*	mg	
✓Potassium Sorbate, NF	mg	
✓Sodium Hydroxide, NF and/or		
✓Lactic Acid, USP		
✓Purified Water, USP		

* Noncompendial ingredient

IV. Analytical Validation

Comment:

- Looking at the summary reports for the assay validation of I and II in human serum, the between and within run accuracy and precision had exactly the same CVs. However, by browsing through the individual tabulations, the actual figures could be determined and have been outlined above. The summaries for the topical and oral formulations were identical, except for the correct LOQ values, this could have been a typographical error while copying files/text. The tabulations for the assay validation is complete and acceptable.

Urine Analysis

Urine samples were analyzed for metronidazole and hydroxymetronidazole (major metabolite) by Urine samples were analyzed after glucuronide hydrolysis. The reported concentrations, therefore, represent the total (unconjugated plus glucuronide conjugates) concentrations of the drug and the metabolite in the urine. In addition to hydroxymetronidazole, urine samples were also analyzed for metronidazole acetic acid, a minor metronidazole metabolite.

The assay validation criteria for the oral formulation assay can be outlined as follows,

V. Pharmacokinetic Studies Overview

The sponsor has submitted one in-vivo single dose comparison study of the marketed 0.75% cream and the 0.75% lotion formulation in healthy adult volunteers and two in-vitro liberation-penetration diffusion cell studies using human cadaver skin comparing the three different topical formulation (lotion vs. gel) in one study and two formulation of the lotion in the other in-vitro study. The sponsor has also quoted a pharmacokinetic/bioavailability study in rosacea patients with Metronidazole Gel, but has not resubmitted the entire study.

In accordance with agreements reached in a telephone conversation on October 20, 1997 with Dr. Bashaw, the sponsor will conduct a pharmacokinetic study in rosacea patients comparing the lotion dosage form with the marketed gel. It is understood by the sponsor in this case that a decision or action taken on the application is not contingent upon the completion of the requested study. A study in patients was also not conducted at the time of the approval of MetroCream® in 1995.

A. In-vivo Studies

a. Single Dose Comparison in Healthy Volunteers (#CR.U9429)

Pharmacokinetic/bioavailability evaluation of topically administered metronidazole cream, 0.75% and metronidazole lotion, 0.75% in healthy adult volunteers.

This study was provided as an interim study report submitted in an amendment to the pending NDA 20-531 for MetroCream® on February 14, 1995. But urine analysis data could not be provided at that time due to lack of a suitably sensitive analytical method for urine analysis. The serum plasma data was reviewed as part of NDA 20-531. The final study report for this study has now been submitted again and includes the urine

data as well as the plasma data originally provided in the MetroCream® NDA amendment.

The plasma data and the study design will be recapitulated briefly again, with more stress on the urine data as it has not been reviewed earlier.

Objectives:

This study was performed with two objectives

- To characterize the pharmacokinetic profile of metronidazole lotion, 0.75% and metronidazole cream, 0.75% dosage forms following a single, topical application in healthy volunteers
- To compare the pharmacokinetics of the lotion and cream to that of the references, a 250 mg oral metronidazole tablet and marketed metronidazole topical gel, 0.75%

Study Design:

The study design has been sketched on page 16 of the Appendix.

Dose administration:

Approximately 1 g (approx 7.5 mg metronidazole) of the cream, lotion or the gel was weighed on weighing boats and applied to the entire face. The administered dose of the topical formulation was determined by multiplying the difference between the before and after application weight by 0.0075. Subjects refrained from washing their face till 24 hrs after application.

The 250 mg oral tablet was administered with 200 mL water.

Data Analysis

The serum concentration-time data following oral and topical administration were analyzed by both noncompartmental and compartmental methods.

Noncompartmental methods

Estimates of C_{max} , T_{max} , latency period, volume of distribution, AUC_{24} and AUC_{∞} for each formulation were determined. Actual time and administered dose were used for all pharmacokinetic calculations. For comparative purposes, C_{max} , AUC_{24} and AUC_{∞} were adjusted to account for differences in the administered dose between treatments. The adjustment was performed by multiplying the parameter, derived as described above, by 7.5 divided by the actual administered oral or topical dose.

The last measurable time point, t , for the 24 hours AUC_{0-t} parameter was based on the observation that only 8 out of 48 sets of serum concentrations had metronidazole

concentrations above the LOQ of ng/mL at time points beyond hrs. Hydroxymetronidazole concentrations were below the limit of quantitation, hence the AUC was not determined for the metabolite.

Accurate estimation of AUC_{∞} following topical administration was hampered by the prolonged absorption phase and lack of quantifiable metronidazole concentrations beyond 24 hrs. Hence λ_z could not be determined by the applicant and the assumption was made that λ_z in each subject remained constant throughout the 21 day study. λ_z from each subjects oral data was used to estimate the residual portion of the AUC_{∞} for topical formulations [This assumption was reasonable based on the fact that metronidazole λ_z or clearance after single oral dose and 7 day multiple oral dose was the same].

All other parameters were calculated in the regular manner.

Compartmental analysis

The metronidazole serum concentration data for each subject following topical administration of the cream, gel and lotion were fitted to a one compartment model with first order input function as described by the following equation:

$$C = \frac{FDK_a}{V(K_e - K_r)} (e^{-k_r(t-t_{lag})} - e^{-k_e(t-t_{lag})})$$

Because of prolonged absorption after topical administration, an accurate estimation of k_e was not possible. The applicant has used the modeling approach suggested by Lima and Jusko. With this approach the V and k_e from the noncompartmental analysis of each subject's oral data were input as constants into the above equation. The assumptions with this approach were that metronidazole clearance remained stable over the 21 day study period and that bioavailability of metronidazole after oral administration is 1. The initial estimate for k_e was determined from the slope of the percent unabsorbed versus time plot. The initial estimate of F was obtained from the dose adjusted ratio of AUC_{∞} after topical and oral administration.

Compartmental analysis of the oral serum concentration-time data was not performed by the applicant due to limited number of observations (≤ 3 time points) available during absorption phase in 9 of the 12 subjects.

The comparative pharmacokinetic parameters for metronidazole and hydroxymetronidazole for the 4 formulations have been tabulated below. The dose adjusted C_{max} was significantly greater ($p < 0.05$) after the oral tablet administration as compared to the three topical dosage forms. In all subjects, the C_{max} after topical administration was $< 30\%$ of the dose-equivalent oral C_{max} . No statistically significant difference in C_{max} was observed among the three topical formulations. As determined from the geometric mean ratios, C_{max} for the topical treatments was 9.7% higher with the cream and 15.6% higher with the lotion as compared to gel. Statistical analysis of the

hydroxymetronidazole C_{max} was not performed due to the occurrence of no quantifiable metabolite serum concentrations in 6 of the 36 sets of serum concentration-time data from the three topical formulations. After adjustment of larger dose, the C_{max} of gel, cream and lotion were 31%, 31% and 34% of the oral C_{max} , respectively.

Metronidazole		Formulation			
Pharmacokinetic parameter	Statistic	Oral	Gel	Cream	Lotion
C_{max} (ng/mL)*	Mean	217.4	29.1	32.9	34.4
	SD	90.6	6.7	10.6	11.4
	CV(%)	41.7	22.8	32.2	33.3
	geometric mean ratio (%)		713.8 (p <0.05)	650.6 (p <0.05)	617.7 (p <0.05)
T_{lag} (hr)	Mean	0.09	0.89	0.81	0.99
	SD	0.17	0.64	0.44	0.91
	CV(%)	193.2	71.18	53.8	92.19
T_{max} (hr)	Mean	1.51	8.51	10.62	9.36
	SD	1.39	2.84	6.82	2.47
	CV(%)	91.47	33.35	64.23	26.38
AUC_{24} (ng.hr/ml)*	Mean	1755.1	555.6	600.0	634.1
	SD	351.7	124.2	185.1	213.1
	CV(%)	20	22.3	30.8	33.6
AUC_{∞} (ng.hr/ml)*	Mean	2016.2	814.8	912.7	971.1
	SD	461.4	251.4	379.7	433.6
	CV(%)	22.9	30.9	41.6	44.6
	geometric mean ratio (%)		250.9 (p <0.05)	231.2 (p <0.05)	218.1 (p <0.05)
Hydroxymetronidazole		Oral	Gel	Cream	Lotion
C_{max} (ng/mL)*	Mean	34.7	10.8	10.7	11.8
	SD	11.7	5.6	5.5	5.9
	CV(%)	33.6	51.8	51.9	49.8
T_{max} (hr)	Mean	8.53	15.27	14.83	17.63
	SD	2.44	6.24	6.60	6.87
	CV(%)	28.58	40.89	44.49	38.96

*standardized to a dose of 7.5 mg by multiplying the calculated value by 7.5/administered dose

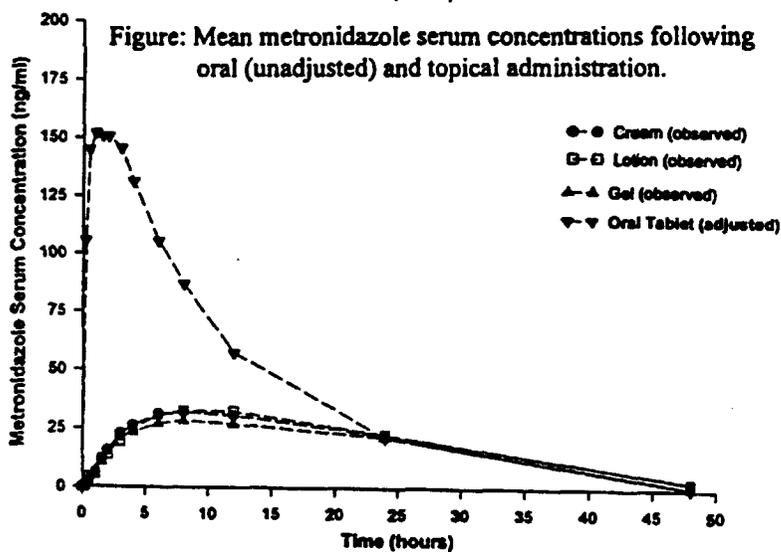
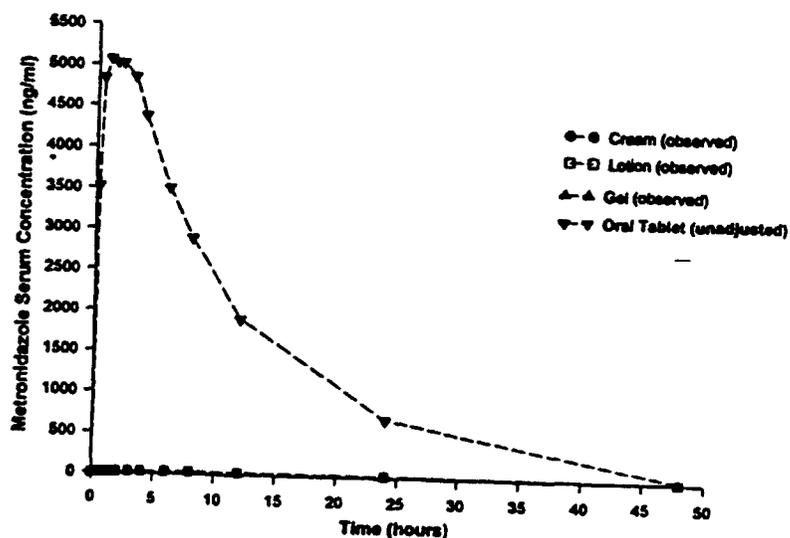


Figure: Mean metronidazole serum concentrations following oral (adjusted) and topical administration.

The metronidazole C_{max} and hydroxymetronidazole C_{max} ranges for the various formulations were as follows:

Formulation	Metronidazole C_{max} ng/mL	Hydroxymetronidazole C_{max} ng/mL
oral tablet		
topical gel		
topical cream		
topical lotion		

The T_{max} for metronidazole ranged from _____ hours for the oral tablet and _____ hours with the three topical formulations. The T_{max} for hydroxymetronidazole varied from _____ hours for the oral tablet and was between _____ hours with the topical formulations.

The metronidazole T_{max} and T_{lag} after topical administration were significantly prolonged as compared to oral. The mean T_{max} occurred 7 hours later with the gel, 9.1 hours later with cream and 7.8 hours later with lotion. The differences in the mean T_{max} and T_{lag} were not significantly different within the three topical formulations.

The slower absorption of metronidazole after topical absorption was also shown by the k_a for the three topical formulations. No significant difference in k_a was observed ($p=0.827$). K_a after oral administration was not determined. Literature reports suggest the k_a s of 1.4 hr⁻¹ to 2.1 hr⁻¹ after oral ingestion. The mean relative bioavailability and absorption rate constants for the topical metronidazole formulations are tabulated below, where F_{AUC} is bioavailability determined from AUC ratios and F_{model} is that obtained by model fitting.

	Gel			Cream			Lotion		
	F_{AUC}	F_{model}	K_a (hr ⁻¹)	F_{AUC}	F_{model}	K_a (hr ⁻¹)	F_{AUC}	F_{model}	K_a (hr ⁻¹)
Mean	0.405	0.412	0.142	0.444	0.445	0.131	0.468	0.474	0.131
SD	0.075	0.079	0.068	0.105	0.083	0.050	0.106	0.101	0.067
CV(%)	18.6	19.2	48.3	23.6	18.6	38.4	22.7	21.4	51.2

The 95% confidence intervals for the ratios of the geometric means for AUC_{∞} indicated that the bioavailability of metronidazole as compared to the oral tablet was between 34-47% for the gel, 37-51% for the cream and 39-54% for the lotion. As compared with the topical gel, the AUC_{∞} was 8.6% higher with the cream and 15.0% higher with the lotion. These differences were not statistically significant. The AUC_{24} was also not significantly different ($p > 0.05$) for the three topical formulations. The comparable extent of metronidazole absorption from the three topical formulations is also supported by the estimate of relative bioavailability determined from the model fitting of the topical serum concentration-time data, F_{model} .

Urinary data:

The mean urinary recovery of metronidazole from the different formulations are tabulated below. Following oral metronidazole administration, approximately 12% of the dose was recovered in the urine over 48 hours as metronidazole and its gluconide conjugate. The urinary recovery of metronidazole was greatest during the 0-6 hour collection interval following oral tablet, as compared to the 12-24 hour collection interval for the topical administration.

Metronidazole		Amount excreted in urine (mg)				
		0-6 hours	6-12 hours	12-24 hours	24-48 hours	48 hour total
Oral	Mean	13.06	8.07	6.21	3.12	30.47
	SD	7.04	2.61	2.24	4.03	12.01
	CV(%)	53.9	32.4	36.0	129.1	39.4
Gel	Mean	0.05	0.082	0.108	0.052	0.292
	SD	0.05	0.045	0.058	0.078	0.178
	CV(%)	99.9	54.9	53.4	151.2	61.0
Cream	Mean	0.054	0.103	0.141	0.063	0.361
	SD	0.044	0.074	0.051	0.100	0.226
	CV(%)	81.9	71.3	36.3	158.9	62.6
Lotion	Mean	0.038	0.111	0.130	0.061	0.340
	SD	0.038	0.058	0.065	0.078	0.168
	CV(%)	99.9	52.1	49.8	128.7	49.3

The mean urinary recovery of the metabolites are tabulated below. Following oral metronidazole administration, approximately 23% was recovered as hydroxymetronidazole and its gluconoride conjugate, and 11% as metronidazole acetic acid and its gluconoride conjugate. These recovery percentages are similar to those reported in literature after oral and intravenous administration. For hydroxymetronidazole, the urinary recovery was greatest during the 12-24 hour collection following oral administration and the 24-48 hour interval following topical administration. This is consistent with the prolonged T_{max} and $T_{1/2}$ with topical administration.

Hydroxy metronidazole		Amount excreted in urine (mg)				
		0-6 hours	6-12 hours	12-24 hours	24-48 hours	48 hour total
Oral	Mean	8.59	14.97	18.14	14.61	56.31
	SD	6.65	5.37	5.72	6.59	19.16
	CV(%)	77.4	35.9	31.6	45.1	34.0
Gel	Mean	0.053	0.094	0.172	0.270	0.589
	SD	0.152	0.082	0.103	0.120	0.303
	CV(%)	286.9	87.1	59.7	44.5	51.4
Cream	Mean	0.027	0.091	0.244	0.314	0.676
	SD	0.048	0.078	0.088	0.107	0.267
	CV(%)	180.0	85.1	36.1	34.1	39.4
Lotion	Mean	0.051	0.117	0.210	0.323	0.700
	SD	0.062	0.048	0.092	0.181	0.252
	CV(%)	121.9	40.9	43.9	55.9	35.9

Metronidazole acetic acid		0-6 hours	6-12 hours	12-24 hours	24-48 hours	48 hour total
Oral	Mean	9.34	8.09	7.87	2.59	27.90
	SD	4.20	2.30	2.04	3.97	8.75
	CV(%)	45.0	28.4	25.9	153.1	31.4

The fraction of the dose recovered in the urine over 48 hours as metronidazole and hydroxymetronidazole was greater after oral administration as compared to topical formulations. The mean ratios between the amounts recovered in the urine after topical and oral administration were 0.345 (range: for the cream and 0.396 (range for the lotion. The individual subject data is attached in the Appendix.

Conclusions

- The rate and extent of metronidazole absorption after topical application of metronidazole cream and lotion are not significantly different from the marketed metronidazole gel in healthy individuals.
- Absorption of metronidazole after topical application of the gel, cream and lotion formulations was less complete and more prolonged than after oral administration.
- The mean relative bioavailability of metronidazole was 44.5% for the cream and 47.4% for the lotion formulation.
- After adjustment of the larger oral dose, the metronidazole C_{max} after topical administration of the cream, gel and lotion was < 30% of the oral C_{max} in all subjects.

Comment

- The applicant at various places of the NDA has mentioned that after adjustment of the larger oral dose, the metronidazole C_{max} after topical administration of the cream, gel and lotion was < 70% of the oral C_{max} in all subjects. By examining the data this does not appear to be true. Also in the NDA 20-531 for MetroCream[®] < 30% of oral C_{max} has been mentioned and restated in the review of the NDA. For the current submission this must have been a misrepresentation of the % amount (i.e < 30% of the oral C_{max} vs. 70% lower than the oral C_{max}).
- By visual inspection of the concentration -time data, the majority of the C_{max} values for metronidazole and hydroxymetronidazole following topical administration did not appear as mentioned in the submission. However, re-analysis of the data gave similar mean and standard deviation values.

B. In-vitro studies

a. **Study Title:** Comparison of in-vitro liberation-penetration of metronidazole applied as two 0.75% (w/w) lotion formulations and as a 0.75% (w/w) commercial gel formulation in the human skin. (# 1.CG.03.SPR.4614).

In-vitro liberation-penetration of the metronidazole lotion used in clinical studies [batch 562.212/2F4] containing propyl gallate was compared to the same lotion [batch 562.208/621] without propyl gallate and to the gel. 10 mg of the formulation were applied to a 1 cm² of excised skin placed in a flow through diffusion cell.

The cumulated quantity of metronidazole recovered in the fluid receptor from 0-15 hours was significantly higher (two fold) with the gel than with both lotions with no apparent reduction in lag time. The steady state flux was estimated around 0.9 $\mu\text{g}\cdot\text{h}^{-1}\cdot\text{cm}^2$ for the gel and 0.3 $\mu\text{g}\cdot\text{h}^{-1}\cdot\text{cm}^2$ for both the lotions. The total cutaneous penetration of metronidazole (including total skin and collected fractions) varied from 14% (for lotions) to 24% of the applied dose (for gel). The total quantity of metronidazole recovered in the receptor fluid varied from 6% to 13% of the applied dose. Kinetic results showed no apparent difference between the two lotions (steady state flux, lag time). The mass balance evaluation indicated an average recovery of 72% for the gel, 71% for metronidazole gel [562.208/621] and 69% for the other lotion [562.212/2F4]. The mean percentages are tabulated below:

Metronidazole Quantification ↓ % of applied dose →	MetroGel	Metronidazole Lotion [562.208/621]	Metronidazole Lotion [562.212/2F4]
Recovery in surface excess and upper cell washing	48%	57%	55%
Total skin	11%	7%	7%
Collected fractions (0-15 hrs)	13%	7%	6%
Total skin + collected fraction	24%	14%	13%
mass balance	72%	71%	68%

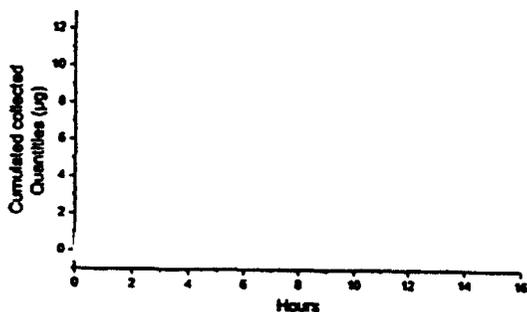


Fig: Cumulated amount collected vs. time plot

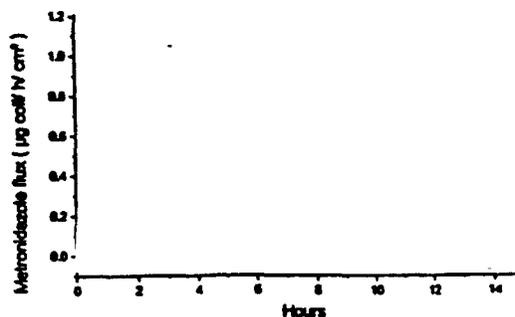


Fig: Flux vs. time plot

b. Study Title: *Comparison of the in-vitro liberation-penetration of metronidazole from two 0.75% (w/w) formulations across human full thickness skin* (#1.CG.03.SUM.4521.INF).

The in-vitro liberation-penetration of metronidazole contained in two different formulations (gel and lotion) at a concentration of 0.75%(w/w) was compared across human non-occluded full thickness skin maintained in dynamic diffusion cells for 15 hours. The gel corresponded to the marketed product under the name of Rozex[®] gel by Lederle (batch 1C19010) and metronidazole lotion is the new formulation (batch 562.203/2F1).

The quantity of metronidazole present in the skin and in the fractions was 3.2 fold higher for the gel than for the lotion. The total cutaneous penetration (skin and collected fraction) of the respected applied quantities of metronidazole was 32% for the gel and 9% for the lotion. The mass balance evaluation indicated an average recovery of 74% of the applied dose for the lotion and 83% of the applied dose for the gel. The mean percentages are tabulated below:

Metronidazole Quantification ↓ % of applied dose →	MetroGel	Metronidazole Lotion
Recovery in surface excess and upper cell washing	50.8 %	65.1%
Total skin	16.9%	6.1%
Collected fractions (0-15 hrs)	14.7%	3.1%
Total skin + collected fraction	31.6%	9.2%
mass balance	83.2%	74.3%

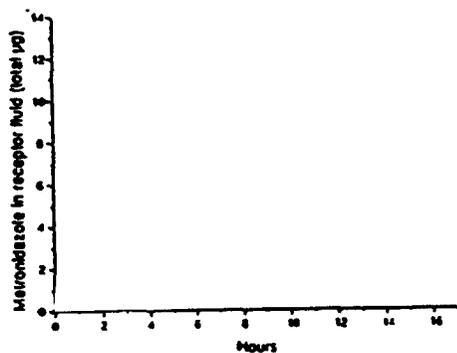


Fig: Cumulated amount collected vs. time plots

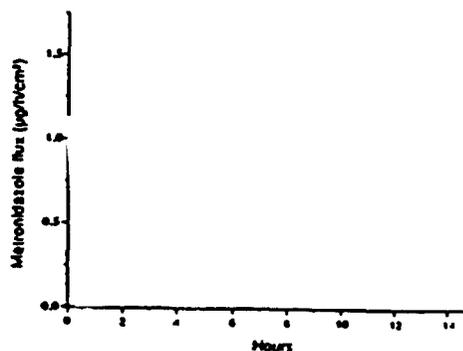


Fig: Flux vs. time plot

VI. Conclusions

The applicant has demonstrated that after topical administration of MetroLotion™ (0.75%), the systemic concentrations of metronidazole are relatively very low (100 times) in serum compared to that after oral administration of a single dose of 250 mg of metronidazole in healthy subjects. The effect of disease state on metronidazole penetration has not been assessed (see recommendation).

Comments (to be sent to the sponsor)

- The following label is recommended for the "Pharmacokinetics" section of the label for MetroLotion™.

Pharmacokinetics

/S/

5/5/98

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. EDB-5/9/98

CC: NDA 20-901
HFD-540/Div File
HFD-540/CSO/Kumerer KOZMA-FORNARO
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy
AE 646 *Murphy*
646 *walker*

APPENDIX

NDA/IND#: 20-901

Volume 1.9

Study Type: Phase I, single dose comparison in healthy volunteers Study # CR.U9429

Study Title: Pharmacokinetic/bioavailability evaluation of topically administered MetroCream and MetroLotion, 0.75% in healthy volunteers.

Study Site	
Clinical Site	Analytical Site

Study Design						
Single Dose	Multiple Dose	Washout Period	Cross-over	Other Designs	Duration	No. of fasted hrs
X		7 days	4 way	open-label randomized		12 hrs before, 3hrs after

Subject Category and Number					
Normal	Patients	Young	Elderly	Renal	Hepatic
X - 12		X			
Subject Type					
Males (N=5)			Females (N=7)		
Age	Weight		Age	Weight	
24-34	135-203 lbs		24-34	107-138 lbs	
Subject Treatment Group					
Group No.	Total No.	Males	Females		
MetroCream	12	5	7		
MetroLotion	12	5	7		
MetroGel	12	5	7		
Flagyl® oral	12	5	7		

Treatment Group	Dose of metronidazole	Dosage Form	Strength	Lot #
MetroCream	7.5 mg (1g applied)	Cream (test)	0.75%	3D0547
MetroLotion	7.5 mg	Lotion (test)	0.75%	HHBZ-3
MetroGel	7.5 mg	Gel (reference)	0.75%	HEBD-1
Flagyl® oral	250 mg	Tablets (reference)	250 mg	3F193

Sampling Times

Plasma: (8 mL)

hrs

Urine: (10 mL)

Table 20A

Urinary Recovery of Metronidazole Following 250 mg Dose of Oral Tablet
Summary of Data For Each Collection Interval and the Total 48 Hour Study Period

Subject	Collection Interval													
	Baseline	0-6 Hour Interval			6-12 Hour Interval			12-24 Hour Interval			24-48 Hour Interval			48 Hour Total
	Conc. (ng/ml)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Amount (mg)
Mean	BQL	24771	636	13.06	23472	419	8.07	11813	662	6.21	2972	1276	3.12	30.47
S.D.		11403	299	7.04	10486	237	2.61	4129	209	2.24	3881	396	4.03	12.01
%CV		46.0	55.9	63.9	44.7	66.6	32.4	34.9	37.8	36.0	130.6	31.1	129.1	39.4
Median	BQL	24242	620	13.9	24089	302	8.01	10743	496	5.94	BQL	1216	BQL	28.60

Conc.: urine concentration
BQL: below the quantifiable limit of the assay

Table 20B

**Urinary Recovery of Hydroxymetronidazole Following 250 mg Dose of Oral Tablet
Summary of Data For Each Collection Interval and the Total 48 Hour Study Period**

Subject	Collection Interval													
	Baseline	0-6 Hour Interval			6-12 Hour Interval			12-24 Hour Interval			24-48 Hour Interval			48 Hour Total
	Conc. (ng/ml)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Amount (mg)
Mean	BQL	17982	636	8.69	49498	419	14.97	36172	662	18.14	12282	1276	14.61	66.31
S.D.		14068	299	6.66	33742	237	6.37	16336	209	6.72	6131	396	6.69	19.16
%CV		78.2	66.9	77.4	68.2	66.6	36.9	46.2	37.8	31.6	41.8	31.1	45.1	34.0
Median	BQL	16928	620	6.46	37041	302	12.88	29646	496	17.66	13194	1216	16.92	64.67

Conc.: urine concentration
BQL: below the quantifiable limit of the assay

Table 20C

Urinary Recovery of Metronidazole Acetic Acid Following 250 mg Dose of Oral Tablet
Summary of Data For Each Collection Interval and the Total 48 Hour Study Period

Subject	Collection Interval													
	Baseline	0-6 Hour Interval			6-12 Hour Interval			12-24 Hour Interval			24-48 Hour Interval			48 Hour Total
	Conc. (ng/ml)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Amount (mg)
Mean	BQL	23198	636	9.34	25967	419	8.09	16218	662	7.87	2866	1276	2.69	27.90
S.D.		22331	299	4.20	16164	237	2.30	7404	209	2.04	4406	396	3.97	8.76
%CV		96.3	66.9	46.0	62.2	66.6	28.4	46.6	37.8	26.9	153.8	31.0	163.1	31.4
Median	BQL	18188	620	9.38	20963	302	8.74	16166	496	8.08	BQL	1216	BQL	29.47

Conc.: urine concentration
BQL: below the quantifiable limit of the assay

Table 21A

Urinary Recovery of Metronidazole Following 1 g Topical Dose of Metronidazole Gel, 0.75%
Summary of Data For Each Collection Interval and the Total 48 Hour Study Period

Subject	Collection Interval													
	Baseline Conc. (ng/ml)	0-6 Hour Interval			6-12 Hour Interval			12-24 Hour Interval			24-48 Hour Interval			48 Hour Total
	Conc. (ng/ml)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Amount (mg)
Mean	BQL	98	598	0.060	216	418	0.082	226	482	0.108	68	1226	0.062	0.292
S.D.		95	349	0.060	118	199	0.046	140	140	0.068	91	411	0.078	0.176
%CV		99.1	58.4	99.9	54.9	47.6	54.9	62.2	29.0	63.4	156.8	33.6	161.2	61.0
Median	BQL	110	646	0.048	196	386	0.090	186	606	0.106	BQL	1080	BQL	0.310

Conc.: urine concentration
BQL: below the quantifiable limit of the assay

Table 21B

Urinary Recovery of Hydroxymetronidazole Following 1 g Topical Dose of Metronidazole Gel, 0.75%
 Summary of Data For Each Collection Interval and the Total 48 Hour Study Period

Subject	Collection Interval												48 Hour Total Amount (mg)	
	Baseline Conc. (ng/ml)	0-6 Hour Interval			6-12 Hour Interval			12-24 Hour Interval			24-48 Hour Interval			
	Conc. (ng/ml)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	
Mean	BQL	66	698	0.053	242	418	0.094	344	482	0.172	242	1228	0.270	0.589
S.D.		146	349	0.162	189	199	0.082	160	140	0.103	132	411	0.120	0.303
%CV		222.8	68.4	286.9	78.0	47.6	87.100	43.7	29.0	59.7	54.6	33.6	44.6	51.4
Median	BQL	BQL	648	BQL	179	385	0.053	308	505	0.148	193	1080	0.224	0.446

Conc.: urine concentration
 BQL: below the quantifiable limit of the assay

Table 22A

Urinary Recovery of Metronidazole Following 1 g Topical Dose of Metronidazole Cream, 0.75%
Summary of Data For Each Collection Interval and the Total 48 Hour Study Period

Subject	Collection Interval													
	Baseline	0-6 Hour Interval			6-12 Hour Interval			12-24 Hour Interval			24-48 Hour Interval			48 Hour Total
	Conc. (ng/ml)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Amount (mg)
Mean	BQL	116	548	0.054	206	529	0.103	246	604	0.141	69	1286	0.063	0.361
S.D.		100	299	0.044	116	319	0.074	105	171	0.051	97	632	0.100	0.226
%CV		86.6	54.6	81.9	56.2	60.3	71.3	42.5	28.3	36.3	164	41.4	168.9	62.6
Median	BQL	121	452	0.074	168	398	0.092	200	598	0.134	BQL	1235	BQL	0.316

Conc.: urine concentration
BQL: below the quantifiable limit of the assay

Table 22B

Urinary Recovery of Hydroxymetronidazole Following 1 g Topical Dose of Metronidazole Cream, 0.75%
 Summary of Data For Each Collection Interval and the Total 48 Hour Study Period

Subject	Collection Interval													
	Baseline	0-6 Hour Interval			6-12 Hour Interval			12-24 Hour Interval			24-48 Hour Interval			48 Hour Total
	Conc. (ng/ml)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Amount (mg)
Mean	BQL	63	648	0.027	246	528	0.091	414	604	0.244	265	1286	0.314	0.676
S.D.		83	299	0.048	273	319	0.078	132	171	0.088	102	632	0.107	0.267
%CV		156.5	54.6	180.0	111.3	60.3	85.1	31.9	28.3	36.100	38.6	41.4	34.1	39.4
Median	BQL	BQL	452	BQL	207	398	0.079	412	598	0.244	265	1235	0.299	0.651

Conc.: urine concentration
 BQL: below the quantifiable limit of the assay

23

Table 23A

Urinary Recovery of Metronidazole Following 1 g Topical Dose of Metronidazole Lotion, 0.75%
 Summary of Data For Each Collection Interval and the Total 48 Hour Study Period

Subject	Collection Interval													
	Baseline	0-6 Hour Interval			6-12 Hour Interval			12-24 Hour Interval			24-48 Hour Interval			48 Hour Total
	Conc. (ng/ml)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Amount (mg)
Mean	BQL	109	603	0.038	241	539	0.111	273	499	0.130	61	1130	0.061	0.340
S.D.		106	406	0.038	117	242	0.068	146	173	0.066	76	327	0.078	0.168
%CV		96.3	67.1	89.9	48.8	44.9	62.1	53.0	34.7	49.8	128.5	29.0	128.7	49.3
Median	BQL	117	446	0.040	246	546	0.114	246	436	0.140	BQL	1110	BQL	0.309

Conc.: urine concentration
 BQL: below the quantifiable limit of the assay
 N.S.: no sample, sample inadvertently discarded after collection

Table 23B

Urinary Recovery of Hydroxymetronidazole Following 1 g Topical Dose of Metronidazole Lotion, 0.75%
 Summary of Data For Each Collection Interval and the Total 48 Hour Study Period

Subject	Collection Interval													
	Baseline	0-6 Hour Interval			6-12 Hour Interval			12-24 Hour Interval			24-48 Hour Interval			48 Hour Total
	Conc. (ng/ml)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Conc. (ng/ml)	Volume (ml)	Amount (mg)	Amount (mg)
Mean	BQL	100	603	0.061	261	639	0.117	446	499	0.210	306	1130	0.323	0.700
S.D.		100	406	0.062	133	242	0.048	226	173	0.092	171	327	0.181	0.262
%CV		100.6	67.1	121.9	63.0	44.9	40.9	60.4	34.7	43.9	66.8	29.0	66.900	36.9
Median	BQL	104	446	0.034	213	646	0.106	426	436	0.232	314	1110	0.364	0.732

Conc.: urine concentration

BQL: below the quantifiable limit of the assay

N.S.: no sample, sample inadvertently discarded after collection

25

Table 24

Total Amount and Fraction of Administered Dose Recovered in Urine Over 48 Hours as Metronidazole and Hydroxymetronidazole Following Oral and Topical Metronidazole Administration

Subject	Oral			Gel			Cream			Lotion		
	Amount Recovered in Urine* (mg)	Fraction of Dose Recovered in Urine*	Amount Recovered in Urine* (mg)	Fraction of Dose Recovered in Urine*	% Urinary Recovery Relative to Oral Dose [†]	Amount Recovered in Urine* (mg)	Fraction of Dose Recovered in Urine*	Urinary Recovery Relative to Oral Dose [†]	Amount Recovered in Urine* (mg)	Fraction of Dose Recovered in Urine*	Urinary Recovery Relative to Oral Dose [†]	
Mean	81.84	0.328	0.83	0.110	0.345	0.98	0.127	0.398	0.98	0.130	0.396	
SD	20.62	0.082	0.33	0.044	0.166	0.34	0.046	0.113	0.32	0.039	0.082	
%CV	25.0	25.0	39.6	40.6	48.1	34.9	36.9	29.1	32.8	29.9	20.8	
Median	76.73	0.307	0.76	0.103	0.349	1.03	0.126	0.413	1.01	0.126	0.403	

Represents amount recovered in urine as metronidazole and hydroxymetronidazole, expressed in metronidazole equivalents

Represents the fraction of dose recovered after topical (gel, cream, or lotion) administration divided by the fraction of dose recovered after oral administration

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-901

ADMINISTRATIVE DOCUMENTS

PATENT AND EXCLUSIVITY INFORMATION (ITEM 13)

Patent Information [21 CFR 314.50 (h) and 314.53 (c)(3)]

1. *Active Ingredient:* Metronidazole, USP
2. *Strength:* 0.75% (7.5 mg/g)
3. *Trade Name:* MetroLotion™ Topical Lotion
4. *Dosage Form and Route of Administration:* Lotion, Topical application to the skin
5. *Applicant Firm Name:* Galderma Laboratories, Inc.

The applicant, Galderma Laboratories, Inc., is a corporate entity doing business in the U.S. at 3000 Alta Mesa Blvd., Suite 300, Fort Worth, TX 76133

6. *Applicable Patent Number(s):*

The applicant, Galderma Laboratories, Inc., believes there are no patents which claim the drug or the drug product or which claim a method of using the drug product covered by this application and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of such patent or patents engaged in the manufacture, use, or sale of the drug or drug product.

November 24, 1997
(Date)

Christine Shank
(Signature)

Christine Shank
Director, Regulatory Submissions
Galderma Laboratories, Inc.

Claimed Exclusivity [21 CFR 314.50 (j)]

1. The applicant, Galderma Laboratories, Inc., claims three (3) years marketing exclusivity upon approval of the drug product that is the subject of this new drug application submitted pursuant to section 505(b) of the FD&C Act.

2. The applicant makes reference to 21 CFR 314.108 (b)(4) in support of this claim.

Claimed Exclusivity - 21 CFR 314.50 (j)(4)

- i. *New clinical investigations*: The applicant certifies that to the best of its knowledge the Phase III safety and efficacy clinical investigation included in the application meets the definition of "new clinical investigation" set forth in 314.108 (a).
- ii. *Essential to approval*: The applicant certifies that it has thoroughly searched the scientific literature and, to the best of the applicant's knowledge, there are no known publications wherein an emollient lotion dosage form of metronidazole in any strength has been studied in the topical treatment of rosacea. Furthermore, publications of clinical investigations with emollient cream dosage forms are with formulations containing metronidazole at higher concentrations (1% to 5%) than the 0.75% strength used for MetroLotion™ Topical Lotion. This is relevant in that the metronidazole in MetroLotion™ Topical Lotion is in solution (dissolved drug substance) while higher concentrations of metronidazole (1% or greater) in either a lotion or cream dosage form would be expected to be in suspension (undissolved drug substance) thus signifying differences in terms of bioavailability. This conclusion is based on the solubility profile of 10 mg metronidazole in 1 mL water at 20°C. Therefore, there are no published studies or publicly available reports to provide sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigation in this application.
- iii. *Conducted or sponsored by*: The applicant certifies that it was the sponsor named in the Form FDA 1571 for Investigational New Drug Application (IND) under which the new clinical investigation that is essential to the approval of this application was conducted.

November 24, 1997
(Date)

Christine Shank
(Signature)

Christine Shank
Director, Regulatory Submissions
Galderma Laboratories, Inc.

d) Did the applicant request exclusivity?

YES // NO /___/

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

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

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO //

If yes, NDA # _____ Drug Name _____
NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO //

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

MA
92

YES // NO /___/
92

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

NDA# 19737 MetroGel, 0.75%
NDA# 20208 MetroGel, 0.75% vaginal
NDA# 20531 Mikrocrom, 0.75%
NDA# 20743 nitrate Cream, 1%

2. Combination product.

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

N/A

YES / / NO / /

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

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

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

YES // NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES // NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES /___/ NO //

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

YES / / NO / /

If yes, explain: _____

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

YES / / NO / /

If yes, explain: _____

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

CR.U9418-The safety and efficacy of 0.75% metronidazole topical lotion for the treatment of rosacea: A randomized, double-blind, vehicle-controlled, parallel comparison.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

YES / /

NO / /

If yes, explain: _____

/S/

11/5/98

Signature

Date

Title:

Project Manager

/S/

11/24/98

Signature of Office/
Division Director

Date

cc: Original NDA 20-901 Division File HFD-540 HFD-93 Mary Ann Holovac
HFD-540/Wright

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

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

NDA/BLA # 20-901 Supplement # Metoprolol Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF 540 Trade and generic names/dosage form (metoprolol) Action: AP AE NA

Applicant Galderna Therapeutic Class 33

Indication(s) previously approved and pediatric use treatment of inflammatory papules

Pediatric information in labeling of approved indication(s) is adequate inadequate
Proposed indication in this application treatment of inflammatory papules

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
 Neonates (Birth-1month) Infants (1month-2yrs) Children (2-12yrs) Adolescents(12-16yrs)

- 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- 3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
 - c. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing,
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, attach memo describing status of discussions.
 - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. See back
- 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? Yes No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from medical review (e.g., medical review, medical officer, team leader)

Signature of Preparer and Title IS/ Project Manager Date 11/5/98

Orig NDA/BLA # 20-901
HF 540 Div File HFD-540/MWright 92 11/24/98
NDA/BLA Action Package
HFD-006/ KRoberts

Rosacea is a relatively common disorder in middle aged adults, not in pediatric patients. This drug has no potential for use in children. Therefore, pediatric studies are not needed.

/S/

PM/998

11/24/98

Date: 5 Nov 1998

The sponsor was asked to provide a listing of all cutaneous adverse dermatologic events regardless of classification to test materials. This information was received via FAX on 3 November 1998 and is presented below:

All Local Cutaneous Dermatologic Adverse Events Regardless of Classification to Test Materials		
	METROLOTION N=71	Vehicle N=70
Local allergic reaction	2 (3%)	0
Contact dermatitis	2 (3%)	1 (1%)
Pruritus (facial)	1 (1%)	0
Skin discomfort(burning and stinging)	1 (1%)	2 (3%)
Erythema	4 (6%)	0
Dry skin(facial)	0	1 (1%)
Condition worse	1 (1%)	7 (10%)
Skin carcinoma	0	2 (3%)
Acne (Sore on nose)	0	1(1%)
Impetigo Ear	0	1(1%)
Infected Cyst	1(1%)	0

The information is consistent with the table of adverse events presented in the clinical review, for all categories except the Dry Skin, Facial. The one adverse event in this category occurred in the vehicle group.

It is recommended that the categories of _____ be removed from the proposed label as these have not routinely been included in labeling as local cutaneous events.

Skin carcinoma is recommended for retention as this informs the pharmacology section of the label which describes increased carcinogenesis in animals.

JS
Susan J. Walker, M.D.
Clinical Team Leader

92 11/17/98



DEPARTMENT OF HEALTH & HUMAN SERVICES

PHILADELPHIA DISTRICT
FOOD AND DRUG ADMINISTRATION
SCIENCE BRANCH

MEMORANDUM

DATE: September 30, 1998

FROM: Lawrence Harmon Jr.

SUBJECT: NDA 20-901

TO: Concepcion Cruz

The subject NDA method has been validated. The Assay and Identification analyses are complete and within specification. No problems or inconsistencies exist within the method.

Lawrence Harmon
Regulatory Chemist

CONSULT #942

LNC TRADEMARK REVIEW

TO: HFD-540

ATTN: Janet G. Higgins

PROPOSED NAME(S): MetroLotion

ESTABLISHED NAME: metronidazole lotion

COMMITTEE'S COMMENTS:

The Committee has no reason to find the proposed name unacceptable.

DL Boring 3/1/98
Dan Boring, Ph.D., Chairman
Labeling and Nomenclature Committee

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-901

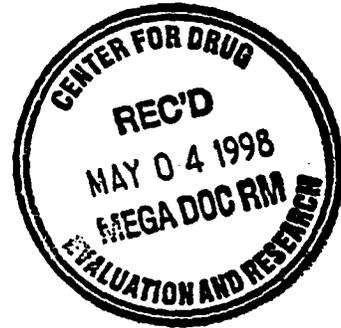
CORRESPONDENCE

SU ✓
ORIG AMENDMENT

ORIGINAL

May 1, 1998

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850



RE: NDA 20-901/Amendment
MetroLotion™ (metronidazole topical lotion) Topical Lotion, 0.75%
4-Month Safety Update Report

Dear Sir or Madam:

The applicant submits herewith the 4-Month Safety Update Report to NDA 20-901 pursuant to 21 CFR 314.50 (d)(5)(vi)(b). The report is comprehensive for all dosage forms of metronidazole and includes information from all U.S.A. and foreign studies.

If there are any questions, please contact me at (817) 263-2676.

Sincere regards,

Christine Shank
Sr. Director, Regulatory Submissions

c: Ms. Susan Kummerer (faxed copy of cover letter only)
Document Control Room (Archival and Clinical Review copies)

ORIGINAL

GALDERMA

2091 AMENDMENT

November 17, 1998

BL

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850



RE: NDA 20-901/Amendment
MetroLotion™ (metronidazole lotion) Topical Lotion, 0.75%
Revised Draft Primary Container Labeling Amendment

Dear Sir or Madam:

Pursuant to a telecon on November 13, 1998 with Ms. Millie Wright, FDA Project Manager, the applicant has revised the primary container labeling for the drug product. At the request of the agency, the following revision was made on the principal display panels of the 0.5 FL OZ, 2 FL OZ, and 4 FL OZ container labels:

The established name for the drug product was changed from (metronidazole topical lotion) to (metronidazole lotion).

Thus, for all labeling components wherein the product tradename and established name appear together, the following naming convention is used:

MetroLotion™ (metronidazole lotion) Topical Lotion, 0.75%.

Please find enclosed mock-ups of the revised (11/98) draft primary container labels. Four sets are provided in the Archival Copy and one set in the Chemistry Review Copy of this submission.

Sincere regards,

Christine Shank

Christine Shank

c: FAX of cover letter to Ms. Mary Jean Kozma-Fornaro

75

ORIGINAL

GALDERMA



NDA 20-901 AMENDMENT

RM



November 3, 1998

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850



RE: NDA 20-901/Amendment
MetroLotion™ (metronidazole topical lotion) Topical Lotion, 0.75%
Response to FDA Request

Dear Sir or Madam:

In response to a fax dated November 2, 1998 from Ms. Mary Jean Kozma-Fornaro, please find on the following pages tabulations of the dermatologic adverse events reported from Clinical Study CR.U9418. The tabulations are briefly identified as follows:

- Table 1 - All cutaneous adverse events regardless of relationship classification to the test materials
- Table 2 - Local cutaneous reactions with an incidence of > 1%
- Table 3 - Treatment-related adverse events

These tabulations exclude patients (MetroLotion), (Vehicle), and (Vehicle) as there were no data collected after Baseline for these patients.

If I can be of further assistance in this regard, please contact me.

Sincere regards,

Christine Shank
Telephone (817) 263-2676
FAX (817) 263-2738

c: Archival and Clinical Review copies to the Document Control Room (HFD-540)
Fax to Ms. Mary Jean Kozma-Fornaro and Ms. Millie Wright

57

DUPLICATE

GALDERMA



NDA ORIG AMENDMENT

BL

October 2, 1998



Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-901/Amendment
MetroLotion™ (metronidazole topical lotion) Topical Lotion, 0.75%
Revised Draft Labeling Amendment

Dear Sir or Madam:

Reference is made to the April 24, 1998 FDA letter wherein comments with respect to review of the chemistry section of the subject application were communicated to the applicant. Three of the review comments were issues specific to the draft labeling for the drug product submitted in the original application. Reference is also made to two FDA Fax Memos dated August 21, 1998 and September 10, 1998 providing Pharmacology/Toxicology review comments on the draft labeling amendment dated July 10, 1998.

The draft labeling provided in this amendment is comprehensive for all changes made since submission of the original new drug application. The applicant has addressed the Chemistry review and Pharmacology/Toxicology review comments and has made other changes and corrections. All revisions and reasons for changes are fully described in the **Summary of Labeling Changes** section of this submission.

The applicant thus submits the requested mock-up versions of the labeling components and typed text for review by all disciplines. An electronic version (diskette) of the Package Insert in WordPerfect 5.x for Windows that is identical in content to the text of the draft Package Insert (revision date September 30, 1998) submitted in this amendment has been forwarded to the FDA Project Manager.

October 2, 1998
NDA 20-901 Draft Labeling Amendment
Page 2 of 2

The Archival Copy contains four sets of the revised draft labeling with one set provided in each review copy.

If there are any questions or comments regarding this submission, please contact me.

Sincere regards,

A handwritten signature in cursive script that reads "Christine Shank".

Christine Shank
Telephone (817) 263-2676

c: DESK COPY to Ms. Millie Wright, FDA Project Manager (HFD-540)

(8)

ORIG AMENDMENT

BT

ORIGINAL
GALDERMA



September 14, 1998



Dr. Carol Vincent
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-901
MetroLotion™ (metronidazole topical lotion) Topical Lotion, 0.75%
Amendment - Microbiology

Dear Dr. Vincent:

This amendment is a formal submission of the change in specification for the finished drug product Microbial Limit Test. The change consists of separate specifications for total aerobic microbial count and total molds and yeasts count and absence of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. This change was discussed this date with Dr. Peter Cooney, FDA Supervisory Microbiologist, and found acceptable.

Please find attached a revised table of tests, specifications, and analytical methods for the drug product incorporating the change in specification for the Microbial Limit Test.

Sincere regards,

Christine Shank
Sr. Director, Regulatory Submissions

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

c: Fax of cover letter to Ms. Millie Wright, Project Manager, HFD-540
Fax of amendment to Dr. Carol Vincent, Microbiologist, HFD-160



BI
ORIG AMENDMENT
ORIGINAL

GALDERMA



August 21, 1998

Dr. Carol K. Vincent
Microbiologist
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850



RE: NDA 20-901
MetroLotion™ (metronidazole topical lotion) Topical Lotion, 0.75%
Amendment - Microbiology

Dear Dr. Vincent:

Pursuant to recent communications and discussions, please find enclosed our response to the issues you raised as a result of your review of the microbiology documentation contained in NDA 20-901 for MetroLotion™ Topical Lotion, 0.75%. We have given a great deal of consideration to the issues and have to the best of our ability attempted to address them in terms of the practical application of regulations, standards, guidelines, etc. relative to topical drug products.

We appreciate the opportunity to work with you.

Field Copy Certification - Pursuant to the requirements of 21 CFR 314.60 (c), the applicant hereby certifies that a complete copy of this amendment has been forwarded to the FDA Dallas District Office, the applicant's home FDA District Office.

Sincere regards,

Christine Shank
Senior Director, Regulatory Submissions

c: Desk copy to Ms. Millie Wright, HFD-540
Archival and Review copies



25

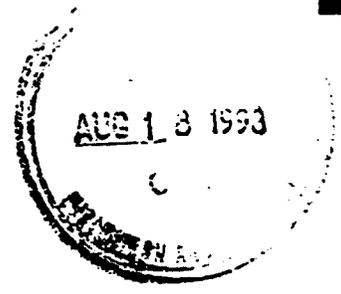
bc

ORIG AMENDMENT

ORIGINAL

August 17, 1998

Dr. William C. Timmer
 Chemist - DNDCIII
 Division of Dermatologic and Dental Drug Products
 Center for Drug Evaluation and Research
 Food and Drug Administration
 Attention: Document Control Room
 9201 Corporate Blvd., HFD-540
 Rockville, Maryland 20850



RE: NDA 20-901
 MetroLotion™ (metronidazole topical lotion) Topical Lotion, 0.75%
Stability Data and Expiration Dating Amendment

Dear Dr. Timmer:

Please find enclosed the 18-month stability data update for the subject drug product. Based on the satisfactory results, the applicant requests a tentative 24 month expiration dating for the commercial drug product. The applicant commits to placing the first three commercial lots on stability and to report the data in the annual reports to the approved NDA.

I sincerely appreciate your consideration of this additional information. If I can be of assistance with any questions, please contact me.

Field Copy Certification

Pursuant to the requirements of 21 CFR 314.60 (c) a complete copy of this amendment is provided to the FDA Dallas District Office, the applicant's home FDA district office. The applicant certifies that the Field Copy is a true copy of the amendment submitted to the unapproved NDA 20-901 for MetroLotion™ (metronidazole topical lotion) Topical Lotion, 0.75%.

Sincere regards,

Christine Shank
 Sr. Director, Regulatory Submissions

Copies to Document Control Room: Archival Copy
 Chemistry Review Copy

Cover Letter to Ms. Millie Wright, FDA Project Manager



BL

July 10, 1998

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850



RE: NDA 20-901/Amendment
MetroLotion™ (metronidazole topical lotion) Topical Lotion, 0.75%
Revised Draft Labeling Amendment

Dear Sir or Madam:

Reference is made to the April 24, 1998 FDA letter wherein comments with respect to review of the chemistry section of the subject application were communicated to the applicant. Three of the review comments were issues specific to the draft labeling for the drug product.

The applicant has revised the labeling to address the chemistry reviewer's comments and in addition has made other changes and corrections that are described in the Summary of Label Changes section of this submission. The applicant thus submits the requested mock-up versions of the labeling components and typed text for review by all disciplines. An electronic version (diskette) of the Package Insert in WordPerfect 5.x for Windows that is identical in content to the text of the draft Package Insert (revision date June 19, 1998) submitted in this amendment has been forwarded to the FDA Project Manager.

The Archival Copy contains four sets of the revised draft labeling with one set provided in each review copy.

If there are any questions or comments regarding this submission, please contact me.

Sincere regards,

Christine Shank

Christine Shank
Telephone (817) 263-2676

c: DESK COPY to Ms. Mary Jean Kozma-Fornaro

DUPLICATE

June 10, 1998

Dr. William C. Timmer
Chemist - DNDCIII
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850



RE: NDA 20-901
MetroLotion™ (metronidazole topical lotion) Topical Lotion, 0.75%
Chemistry, Manufacturing, and Controls Amendment

Dear Dr. Timmer:

Pursuant to 21 CFR 314.60 (a) the applicant submits herewith an amendment to the subject unapproved new drug application in response to comments received in a FDA letter dated April 24, 1998. Reference is also made to a telecon on May 6, 1998 wherein the applicant discussed the review comments with yourself and Dr. Tony Decamp.

With the exception of the comments relating to the proposed labeling for the drug product, a complete response is provided to each of the technical comments. As was agreed in the telecon, the applicant will prepare and submit a separate amendment to address the labeling issues.

If you should have any questions or need further clarification with respect to any of the responses, please contact me. I appreciate the opportunity to work with you to help resolve any concerns.

Field Copy Certification

Pursuant to the requirements of 21 CFR 314.60 (c) a complete copy of this amendment is provided to the FDA Dallas District Office, the applicant's home FDA district office. The applicant certifies that the Field Copy is a true copy of the amendment submitted to the unapproved NDA 20-901 for MetroLotion™ (metronidazole topical lotion) Topical Lotion, 0.75%.

Sincere regards,

A handwritten signature in cursive script that reads "Christine Shank".

Christine Shank
Sr. Director, Regulatory Submissions

Copies to Document Control Room: Archival, Chemistry Review, 2 copies of Samples and Methods Validation Package

NE
ORIGINAL

April 9, 1998

Ms. Susan Kummerer
Project Manager
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850



RE: NDA 20-901
METROLOTION™ (metronidazole topical lotion) Topical Lotion, 0.75%
Electronic Diskette - Clinical Study Report CR.U9418

Dear Susan:

Pursuant to a telephone call I received today from Ms. Mary Jean Kozma-Fornaro, I am providing an electronic version of the clinical study report for CR.U9418 as per a request by the biostatistician. The enclosed diskette is formatted in WordPerfect 5.2 for Windows 95. I hope this will be satisfactory, however, if there are any problems, please contact me and we will try to work out a solution. I can certify that the text is identical to the text of the report in hard copy provided in the original NDA submission. What I cannot certify is that the original format will be retained if a different software version or printer is used than what was used to generate the original hard copy.

Please also be advised that this electronic version does not contain the tables that were generated from the SAS datasets (previously provided).

An archival copy of this correspondence and a signed Form FDA 356h is submitted to the NDA file. Your copy only contains the diskette.

If I can be of further assistance, please contact me.

Sincere regards,

Christine Shank
Telephone (817) 263-2676



ORIGINAL

March 25, 1998

Phyllis A. Huene, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

BM
ORIG AMENDMENT

RE: NDA 20-901
MetroLotion™ (metronidazole topical lotion) Topical Lotion, 0.75%
Amendment - Response to Clinical Review Request for Information

Dear Dr. Huene:

Reference is made to a facsimile transmission dated March 16, 1998 from Ms. Susan Kummerer and to a teleconference on March 23, 1998 between yourself and Ms. Susan Kummerer, and Dr. Michael Tuley and Ms. Bobbi Woodward of Galderma Laboratories, Inc.

Pursuant to the facsimile request and the subsequent discussions, the sponsor submits herewith additional summary information of the safety data for Clinical Study CR.U9418. Table 1, attached, provides Baseline and Maximum Follow-up scores for each parameter and treatment.

The results demonstrate there were no significant differences between MetroLotion and Vehicle at Baseline for any of the parameters listed in Table 1. Both treatments reduced the dryness and erythema based on the change from Baseline to the Maximum Follow-up score. There was no change for either treatment with respect to burning, pruritus, and telangiectasia from Baseline to the Maximum Follow-up score. There were no significant differences between MetroLotion and Vehicle in the Maximum Follow-up scores for burning, dryness, pruritus and telangiectasia. However, there was significantly ($p < 0.05$) less erythema for subjects using MetroLotion during the trial than Vehicle treated subjects.

In conclusion, neither MetroLotion nor its Vehicle caused any increase in burning, pruritus, or telangiectasia. Both MetroLotion and its Vehicle reduced the dryness associated with rosacea. And, MetroLotion reduced erythema.

Phyllis A. Huene, M.D.
March 25, 1998
Page 2 of 2

We appreciate this opportunity to assist you with your review. If you have further questions or if we can assist in any other way, please contact us.

Sincere regards,

A handwritten signature in cursive script that reads "Christine Shank".

Christine Shank

Attachment

c: Ms. Susan Kummerer (faxed copy of correspondence)
Dr. Michael Tuley