

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20-901

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-901

Trade Name: MetroLotion Topical Lotion, 0.75%

Generic Name:(metronidazole)

Sponsor: Galderma Laboratories, Inc.

Approval Date: November 24, 1998

Indication: Provides for the use of MetroLotion (metronidazole lotion) Topical Lotion, 0.75%, for treatment of inflammatory papules and pustules of rosacea

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Application Number: NDA 20-901

APPROVAL LETTER



Food and Drug Administration
Rockville MD 20857

NDA 20-901

NOV 24 1998

Galderma Laboratories, Inc.
Attention: Christine E. Shank
Senior Director, Regulatory Submissions
3000 Alta Mesa Boulevard, Suite 300
Fort Worth, Texas 76133

Dear Ms. Shank:

Please refer to your new drug application (NDA) dated November 28, 1997, received December 2, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MetroLotion™ (metronidazole lotion) Topical Lotion, 0.75%.

We acknowledge receipt of your submissions dated January 15, February 9 and 12, March 25, April 9, May 1, June 10, July 10, August 17 and 21, September 14 and 15, October 2, and November 3, 17, 19 and 23, 1998.

This new drug application provides for the use of MetroLotion™ (metronidazole lotion) Topical Lotion, 0.75%, for treatment of inflammatory papules and pustules of rosacea.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for package insert and immediate container labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-901." Approval of this submission by FDA is not required before the labeling is used.

We remind you that any drug product lot which was the result of the reprocessing procedure, described on page 5 of the June 10, 1998 submission, should not be released for marketing prior to approval of a supplement requesting this reprocessing procedure.

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Page 2

We understand that the pharmacokinetic study of this formulation on diseased subjects is complete, and the study report will be submitted by March, 1999.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Millie Wright, Project Manager, at (301)827-2020.

Sincerely,



Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-901

MEDICAL REVIEW(S)

NOV - 5 1995

MEDICAL OFFICER'S REVIEW OF NDA 20-901
ORIGINAL SUBMISSION

May 4, 1998

SPONSOR: Galderma Laboratories
Fort Worth, Texas

DRUG: Metronidazole lotion 0.75%

PROPOSED TRADE NAME: Metro lotion

CLINICAL INDICATION: Rosacea

Proposed labeling indication statement: "for topical application in the treatment of inflammatory papules and pustules of rosacea."

DOSAGE AND ADMINISTRATION: Applications BID.

FORMULATION:

✓ Metronidazole	0.75%
✓ Carbomer 941	%
✓ Glycerin	%
✓ Polyethylene glycol 400	%
✓ Benzyl alcohol	%
✓ Steareth-21	%
✓ Glyceryl stearate and PEG-100 stearate	%
✓ Stearyl alcohol	%
✓ Light mineral oil	%
✓ Cyclomethicone	%
✓ Potassium sorbate	%
✓ Sodium hydroxide and/or lactic acid	
✓ Purified water	

DATE OF SUBMISSION: November 28, 1997

RELATED SUBMISSIONS: IND NDA 19-737 for MetroGel 0.75%; NDA 20-531 for MetroCream 0.75%, approved November 1988 and September 1995, respectively, for twice daily application in the treatment of rosacea.

PHARMACOLOGY AND CONTROLS REVIEWS: These are currently pending.

Rationale for use

Metronidazole lotion 0.75% was developed as a line extension to the marketed metronidazole cream and gel formulations.

Foreign marketing history

Metronidazole lotion is not being marketed in any foreign country, nor has it been withdrawn from marketing in any foreign country. To the best of the sponsor's knowledge, the drug in any strength or dosage form has not been withdrawn from marketing in any country for reasons of safety.

FDA-sponsor agreements

At a meeting on May 9, 1994 between the sponsor and the Agency, it was agreed that a single clinical safety and efficacy study would be sufficient to support the application for Metronidazole lotion 0.75%.

Product formulation used in clinical studies

The formulation for 0.75% metronidazole lotion used in the clinical studies differed from the proposed commercial formulation by the addition of _____%. It is felt by this reviewer that the difference in formulations is not significant.

Cutaneous safety studies

1. **Cumulative irritancy potential.** This study was a randomized, single blind trial on 25 normal subjects, performed by A. Parneix-Spake, M.D. and J.J. Thebault, M.D., Paris, France. The test materials were metronidazole lotion 0.75% and the lotion vehicle. Applications of the test materials were made under occlusive patches to the same skin sites on the back, daily for five days each week for three weeks. The patches remained in place for 24 hours each day during the week and for 72 hours during each weekend. At each patch removal the test sites were scored for reactions on the following scale.

0	=	no erythema
0.5	=	barely perceptible erythema
1	=	mild erythema, with or without edema
2	=	moderate erythema, edema, with or without papules
3	=	important erythema, edema, with or without papules
4	=	important erythema, edema, vesicles or blisters

A Mean Cumulative Irritancy Index was calculated for each material, and classification was made according to the following scale.

Mean Cumulative Irritancy Index	Classification
< 0.25 and 0.25 inclusive	Non irritant
0.25 (non inclusive) to 1	Slightly irritant
1 (non inclusive) to 2	Moderately irritant
2 (non inclusive) to 3	Very irritant
3 (non inclusive) to 4	Extremely severe irritant

Results were as follows.

Local events were a moderate pruritus in one subject on the active lotion, mild to moderate pruritus in 3 subjects on the vehicle, and mild pruritus in one subject with both test materials; all were on one occasion only and were transient in nature.

The Mean Cumulative Irritancy Indexes were as follows.

	MCII	Classification
Metronidazole lotion	0.03	Non irritant
Lotion vehicle	0.06	Non irritant

The individual scores for metronidazole lotion showed that two subjects had a score of 0.5 on at least one occasion, and three subjects had a score of 1.0 on at least one occasion; there were no reactions with metronidazole lotion in the other subjects at any time.

2. Contact sensitization. This was performed by

Enrolled into the study were 233 subjects, of which 216 completed both phases.

In the induction phase, applications of Metronidazole lotion 0.75% and the lotion vehicle were made in a double blind, randomized manner to the same skin site on the back of each subject under occlusive patches three times weekly for three weeks. Each patch remained in place for 48 hours. Reactions were scored at 48 hours after the Monday and Wednesday application and at 72 hours after the Friday application. After a two week rest period a challenge patch was applied to a new skin site and remained in place for 48 hours. Reactions were scored at 48 and 96 hours after application in the challenge phase.

The scale used for scoring reactions in both phases was as follows.

0	=	no visible reaction and/or erythema
1	=	mild reaction - macular erythema (faint, but definite pink)
2	=	moderate reaction- macular erythema (definite redness, similar to a sunburn)
3	=	strong to severe reaction - macular erythema (very intense redness)

Letter grades were appended to numerical grades if appropriate; these were defined as follows.

E	=	Edema - swelling, spongy feeling when palpated
P	=	Papules - red, solid, pinpoint elevations, granular feeling, diameter 5 mm or less
V	=	Vesicles - small elevation containing serous fluid (blister-like), diameter 5 mm or less
B	=	Bulla reaction - fluid-filled lesion greater than 5 mm in diameter
S	=	Spreading - evidence of the reaction beyond the patch site
W	=	Weeping - result of a vesicular or bulla reaction - serous exudate - clear fluid oozing or covering patch site
I	=	Induration - solid, elevated, hardened, thickening skin reaction

Superficial changes such as glazing, peeling, or pigmentary changes were also noted.

Results were as follows.

Two subjects showed reactions during the induction phase but not at challenge; these were mild erythema which did not recur with repeated exposure. One subject had a reaction during the challenge phase only; this was a mild erythema with both test materials. Three subjects had reactions both during the induction and challenge phases, and were rechallenged at seven weeks following the first challenge with the following individual components of the vehicle:

% benzyl alcohol
 % PEG 400
 %
 % potassium sorbate
 % Steareth-21
 % Cyclomethicone

The reactions in these subjects are described as follows.

1. Subject had a mild erythema with both test materials at the last induction patch, and with the challenge patch had mild to moderate erythema with papules with both test materials at the 48 and 96 hour readings. On rechallenge with the individual vehicle components this subject had a reaction to benzyl alcohol consisting of mild to moderate erythema with papules through the 96 hour reading. None of the other components elicited a reaction. It was concluded that this subject was sensitized to benzyl alcohol.
2. Subject had a mild erythema and papules with both test materials at the fourth induction patch, which progressed to moderate erythema with vesiculation and scabbing by the 8th application. On rechallenge a strong reaction, consisting of marked erythema with edema and vesiculation, was observed with both test materials until a 120 hour reading. At rechallenge with the individual components reactions to benzyl alcohol were found, consisting of moderate macular erythema with edema, vesicles, and evidence of spreading. No reactions were found with the other individual components. The conclusion was that this subject was sensitized to benzyl alcohol..
3. Subject had moderate erythema with vesicles with both test materials at the second induction patch, and the last three induction patches were omitted because of the reactions. On challenge there were mild papules with both test materials through the 96 hour reading. On rechallenge with the individual components there was a mild erythema with papules through the 96 hour reading with benzyl alcohol, and a mild erythema with potassium sorbate at the 24 and 48 hour readings. The conclusion was that this subject was sensitized to benzyl alcohol.

The sponsor's overall conclusion is that Metronidazole lotion and its vehicle were non-irritating in 215 of the 216 subjects tested, with one subject showing mild irritation with both products at challenge. Three of the subjects had an allergic contact dermatitis response to benzyl alcohol; two of these probably had been sensitized to benzyl alcohol prior to participation in the study.

3. Phototoxicity potential. This was a single blind, randomized study conducted on 12 subjects by C. Queille-Roussel, Nice, France. Duplicate applications of Metronidazole lotion 0.75% and the lotion vehicle were made under occlusive patches to contralateral skin sites of the back. Untreated control patches were applied to adjacent skin sites. After 6 hours all patches were removed, and one set of patch sites were irradiated with 20 Joules/cm² of UVA radiation from a Xenon solar simulator with a filtered light source. The other set of patch sites served as non-irradiated control sites.

The sites were scored at one hour after irradiation and at 24, 48 and 72 hours post-irradiation, using the following scale.

0	=	no erythema
0.5	=	equivocal erythema
1	=	slight erythema with or without edema
2	=	moderate erythema, edema with or without papules
3	=	severe erythema, edema with or without papules
4	=	severe erythema, edema, vesicles or bullae

Results were that with metronidazole lotion, scores of 0.5 were found at irradiated sites in 4 subjects. Scores of 1 were found at the central irradiated area at vehicle and untreated sites in 2 subjects, which was felt to be possibly a slight UVA induced erythema. No subject displayed what was considered to be a phototoxic reaction.

The sponsor's conclusion was that under the conditions of this study neither metronidazole lotion or its vehicle demonstrated a potential for phototoxicity.

4. Photosensitization potential. This was a single blind, randomized study, conducted on 25 subjects by C. Queille-Roussel, Nice, France.

During the induction phase, applications of Metronidazole lotion 0.75% and the lotion vehicle were made under occlusive patches to skin sites on the back of each subject, remaining in place for 24 hours; this was done six times (twice weekly) over a three week period. After each patch removal the sites were irradiated with 3 MEDs of UVA + UVB radiation. During this phase, reactions were scored on the following scale.

0	=	no reaction
0.5	=	equivocal reaction
1	=	slight
2	=	moderate
3	=	marked
4	=	severe

After a 14 day rest period duplicate challenge patches with each material were applied to naive skin sites for 24 hours. At patch removal one set of skin sites was irradiated with 4 Joules/cm² of UVA radiation from a Xenon lamp. An additional untreated patch site was irradiated and served as an irradiated control site.

The sites were scored for reactions at 24, 48, and 72 hours post-irradiation, using the following scale.

0	=	no reaction
0.5	=	erythema on a part of the test site, doubtful reaction
1	=	erythema covering the test site
2	=	erythema and induration covering the whole test site
3	=	erythema, induration, and vesicles covering the test site
4	=	erythema, induration, vesicles and/or bullae covering the test site

Results during the induction phase at the metronidazole sites were that most subjects showed a maximum reaction of grade 2 (moderate), and 4 subjects had a grade 3 (marked) reaction. The metronidazole lotion sites showed somewhat lower scores than did the placebo and untreated sites, as seen in the following table of the distribution of total scores.

Scores - Induction phase						
	0	0.5	1	2	3	4
Placebo	24	22	43	166	19	0
Metronidazole lotion	29	51	65	121	8	0
Untreated	25	22	46	159	22	0

The distribution of scores during the challenge phase was as follows.

Scores - Challenge phase						
	0	0.5	1	2	3	4
Irradiated side						
Placebo	72	3	0	0	0	0
Metronidazole lotion	71	4	0	0	0	0
Untreated	66	9	0	0	0	0
Non-irradiated side						
Placebo	75	0	0	0	0	0
Metronidazole lotion	75	0	0	0	0	0
Untreated	72	3	0	0	0	0

There were no reactions of an allergic or photoallergic nature in any of the 25 subjects. The sponsor's conclusion was that, under the conditions of this study, the metronidazole lotion did not show a potential for photoallergy.

Reviewer's comments: It is felt that the cutaneous safety studies have been adequately performed, and demonstrate that Metronidazole lotion 0.75% has low potential for irritation, sensitization, phototoxicity, or photosensitization. (It is, however, noted that in phototoxicity studies the test material usually remains in contact with the skin for 24 hours.)

Pivotal clinical effectiveness study (Study CR.U9418)

The investigators for this study were as follows.

Debra Breneman, M.D. Cincinnati, OH	Alicia Bucko, D.O. Fort Worth, TX
David Friedman, M.D. Providence, RI	Elyse Rafal, M.D. East Setauket, NY
Sewon Kang, M.D. Ann Arbor, MI	J. Michael Maloney, M.D. Denver, CO

- 1) Study objective: This was to evaluate the safety and effectiveness of metronidazole topical lotion 0.75%, when applied twice daily for 12 weeks in patients with moderate to severe rosacea.
- 2) Study design: This was a double blind, randomized, multicenter comparison of metronidazole lotion 0.75% and its vehicle in patients with rosacea.
- 3) Inclusion criteria: Those enrolled were males and females over 18 years of age, diagnosed with moderate to severe rosacea, as shown by the presence of at least 6 but not more than a total of 50 papules and/or pustules, moderate to severe erythema, and telangiectasia.
- 4) Exclusion criteria: Patients were excluded from enrollment into the study for the following reasons.
 - Concomitant dermatologic disorder(s) which would preclude accurate evaluation of the rosacea, such as acne vulgaris, facial psoriasis, secondary acne, acne conglobata, acne fulminans, facial seborrhea, etc.
 - A significant medical disorder which would preclude accurate evaluation of the rosacea.
 - Ocular rosacea of sufficient severity to require topical or systemic antibiotics.

- Administration of systemic antibiotics within one month of study entry or topical antibiotics within two weeks of study entry.
- Concurrent antibiotic therapy in any formulation (topical or systemic).
- Administration of systemic corticosteroids within one month of study entry or topical corticosteroids within two weeks of study entry.
- Concurrent use of corticosteroid therapy in any formulation (systemic or topical).
- Administration of any systemic medication for the treatment of rosacea within one month of study entry or any topical medications for the treatment of rosacea within two weeks of study entry.
- Administration of systemic isotretinoin within six months of study entry or topical retinoids within four weeks of study entry.
- Concurrent anticoagulation therapy, e.g. Coumadin, heparin.
- Concurrent chronic anti-inflammatory treatment in any formulation (topical or systemic). Occasional NSAIDs were acceptable.
- A history of hypersensitivity to metronidazole.
- A history of blood dyscrasias.
- Pregnant women or nursing mothers.
- Non-use of an effective method of contraception.
- Administration of laser surgery to the facial area for telangiectasia or other condition within six weeks prior to study entry.
- Use of a sauna within two weeks prior to study entry.

5) Treatment regimen. Applications were made twice daily to the face for 12 weeks. ✓
The patients were instructed as follows in regard to their treatment.

1. Apply a thin layer of medication two times daily; once in the morning and once in the evening to the ENTIRE facial area (nose, cheeks, forehead, and chin).
2. Apply the study medication after cleansing, bathing, or showering. Use the supplied Cetaphil Cleansing lotion to wash your face. Otherwise, do not change your regular cleansing habits during the study.
3. You are allowed to use cosmetics once the study medication has been applied and given adequate time to dry (at least five minutes).
4. Avoid contact with the eyes or surrounding skin.
5. If at some point during the study you feel like using a moisturizer on your face, contact your doctor or study coordinator. They will supply you with Nutraderm 30 lotion.

It is very important that you wait to use the Nutraderm 30 lotion at least 5-10 minutes after treating with the study medication. No moisturizer should be used within two hours of treating with the study medication.

It is important that you avoid the following foods and beverages throughout the study: spicy foods, thermally hot foods and drinks, alcoholic beverages and caffeine.

6) Effectiveness parameters. The patients returned every three weeks for evaluation of the following parameters.

a. Lesion counts for inflammatory lesions (papules and pustules).

b. Clinical signs: Erythema and telangiectasia were evaluated on the following scales. (Although it is not so stated by the sponsor, these categories appear to have been given numerical scores of 0, 1, 2, and 3 for the purpose of analysis.)

Erythema	
Absent	minimal residual or no perceptible erythema.
Mild	slight erythema with either restricted central involvement or generalized whole face.
Moderate	pronounced erythema with either restricted central involvement or generalized whole face.
Severe	severe erythema or red-purple hue with either restricted central involvement or generalized whole face.

Telangiectasia	
Absent	no telangiectasia.
Mild	slight telangiectasia characterized by appearance of a few, fine, small red vessels (0.2 mm or less in diameter); telangiectasia covers less than 10% of face.
Moderate	pronounced telangiectasia characterized by appearance of several fine and/or a few large vessels (0.2 mm or greater in diameter); telangiectasia covers between 10-30% of face.
Severe	severe telangiectasia characterized by appearance of many fine and/or large vessels; telangiectasia covers greater than 30% of face.

c. Investigator's global assessment of improvement. This was evaluated on the following scale.

Investigator's global assessment	
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

7) Safety evaluation. At each visit subjective assessments of stinging/burning, pruritus, and dryness were graded as none, mild, moderate or severe. These categories were defined for stinging/burning and pruritus as follows.

Stinging/burning	
None	
Mild	slight warm, tingling/stinging sensation; not really bothersome
Moderate	definite warm, tingling/stinging sensation that is quite bothersome
Severe	warm to hot, tingling/stinging sensation that has caused definite discomfort

Pruritus	
None	
Mild	slight itching; not really bothersome.
Moderate	definite itching that is somewhat bothersome.
Severe	intense itching that has caused pronounced discomfort to the patient. Excoriations may be present.

Systemic safety was monitored at two of the six centers, with the following parameters evaluated at baseline and week 12.

- Hematology: hematocrit, hemoglobin, RBC, WBC and differential, platelet counts.
- Chemistries: protein, albumin, globulin, bilirubin, SGPT, SGOT, alkaline phosphatase, lactic dehydrogenase, BUN, creatinine, uric acid, calcium, phosphate, cholesterol, triglycerides, glucose, sodium, potassium, chloride, CO₂.
- Urinalysis with microscopic examination.

Results were as follows.

- 1) Demographic characteristics: 144 patients were enrolled in the study, of which 125 patients completed the 12 week treatment period. The demographic characteristics and baseline disease severity of all patients enrolled were as follows.

DEMOGRAPHIC AND DISEASE CHARACTERISTICS		
	Metro lotion	Vehicle
Sex		
Male	16 (22%)	21 (29%)
Female	56 (78%)	51 (71%)
Race		
White	70 (97%)	70 (97%)
Black	1 (1%)	2 (3%)
Hispanic	1 (1%)	0
Age		
Mean	47.8	46.9
Range		
Disease severity		
Moderate	58 (81%)	59 (82%)
Severe	14 (19%)	13 (18%)

- 2) Patient disposition and evaluability: All 144 patients had at least one treatment application and were included in the intent-to-treat and the safety analyses. Forty-two patients had deviations from the protocol and were considered nonevaluable at certain visits; these comprised 18 on metronidazole lotion and 24 on the vehicle. The numbers of patients that were evaluable at each visit was as follows.

Patients evaluable for efficacy		
	Metro lotion (72 pts enrolled)	Vehicle (72 pts enrolled)
Baseline	66 (92%)	62 (86%)
Week 3	66 (92%)	59 (82%)
Week 6	57 (79%)	58 (81%)
Week 9	59 (82%)	54 (75%)
Week 12	56 (78%)	49 (68%)

The reasons for nonevaluability were as follows.

Reasons for non evaluability		
	Metronidazole lotion	Vehicle
Concomitant medication	6	10
Dropped before week 3	2	4
Non-compliance	1	0
Protocol violation	1	2
Visit windows > 7 days	8	8

In addition, 19 patients were discontinued from the study for the following reasons.

Patient discontinuations		
	Metronidazole lotion	Vehicle
Medical event	5	7
Patient request	0	3
Protocol violation	1	2
Lost to followup	1	0
Total	7	12

3) Efficacy evaluation. The results are provided for baseline, each return visit, and at endpoint. Endpoint was the last evaluation conducted for a given point after the baseline evaluation.

The results for the efficacy evaluable patients were as follows.

a. Lesion counts.

The mean inflammatory lesion counts and the mean change from baseline in inflammatory lesion counts at each evaluation time were as follows.

MEAN INFLAMMATORY LESION COUNTS Efficacy evaluable patients					
	Metronidazole lotion		Vehicle		p value
	# pts	Mean	# pts	Mean	
Baseline	66	15.8	62	16.1	0.696
Week 3	66	10.6	59	13.6	0.004
Week 6	57	8.1	58	12.7	0.000
Week 9	59	6.5	54	11.0	0.000
Week 12	56	6.7	49	11.7	0.000
Endpoint	66	6.8	62	11.8	0.000

MEAN PERCENT CHANGE IN INFLAMMATORY LESION COUNTS Efficacy evaluable patients					
	Metronidazole lotion		Vehicle		p value
	# pts	Mean	# pts	Mean	
Week 3	66	- 31.2	59	- 12.3	0.036
Week 6	57	- 44.2	58	- 17.5	0.000
Week 9	59	- 55.2	54	- 25.8	0.000
Week 12	56	- 55.4	49	- 21.9	0.000
Endpoint	66	- 52.1	62	- 22.4	0.000

a. Other clinical signs.

The mean scores for erythema and telangiectasis at each evaluation time were as follows.

ERYTHEMA					
Efficacy evaluable patients					
	Metronidazole lotion		Vehicle		p value
	# pts	Mean	# pts	Mean	
Baseline	66	2.3	62	2.3	0.326
Week 3	66	1.9	59	2.0	0.120
Week 6	57	1.7	58	1.9	0.595
Week 9	59	1.5	54	1.6	0.359
Week 12	56	1.5	49	1.7	0.375
Endpoint	66	1.5	62	1.7	0.173

TELANGIECTASIA					
Efficacy evaluable patients					
	Metronidazole lotion		Vehicle		p value
	# pts	Mean	# pts	Mean	
Baseline	66	1.5	62	1.6	0.093
Week 3	66	1.4	59	1.6	0.033
Week 6	57	1.4	58	1.6	0.025
Week 9	59	1.3	54	1.5	0.062
Week 12	56	1.3	49	1.5	0.039
Endpoint	66	1.3	62	1.6	0.032

c. Investigator's global assessment. The global assessment at week 12 and at endpoint were as follows.

INVESTIGATOR'S GLOBAL EVALUATION Efficacy evaluable patients			
	Metronidazole lotion	Vehicle	p value
Week 12			
Clear	5 (8.9%)	0	0.000
Marked improvement	18 (32.1%)	11 (22.4%)	
Definite improvement	17 (30.4%)	9 (18.4%)	
Minimal improvement	6 (10.7%)	10 (20.4%)	
No change	8 (14.3%)	11 (22.4%)	
Worse	2 (3.6%)	8 (16.3%)	
Endpoint			
Clear	5 (7.6%)	0	0.000
Marked improvement	18 (27.3%)	11 (17.7%)	
Definite improvement	20 (30.3%)	10 (16.1%)	
Minimal improvement	10 (15.2%)	14 (22.6%)	
No change	9 (13.6%)	18 (29.0%)	
Worse	4 (6.1%)	9 (14.5%)	

The percentage of patients with an assessment of definite improvement, marked improvement, or clear at each visit was as follows.

PATIENTS WITH DEFINITE IMPROVEMENT, MARKED IMPROVEMENT, OR CLEAR Efficacy evaluable patients			
	Metronidazole lotion	Vehicle	p value
Week 3	30.3%	10.2%	< 0.01
Week 6	49.1%	20.7%	< 0.01
Week 9	66.1%	38.9%	< 0.01
Week 12	71.4%	40.8%	< 0.01
Endpoint	65.2%	33.9%	< 0.01

The results for the intent-to-treat patients were as follows.

a. Lesion counts.

The mean inflammatory lesion counts and the mean change from baseline in inflammatory lesion counts at each evaluation time were as follows.

MEAN INFLAMMATORY LESION COUNTS Intent-to-treat patients					
	Metronidazole lotion		Vehicle		p value
	# pts	Mean	# pts	Mean	
Baseline	72	15.5	72	16.2	0.640
Week 3	71	10.4	68	13.9	0.001
Week 6	66	7.7	64	13.0	0.000
Week 9	66	6.3	60	11.6	0.000
Week 12	65	6.6	60	12.5	0.000
Endpoint	72	6.8	72	12.9	0.000

MEAN PERCENT CHANGE IN INFLAMMATORY LESION COUNTS Intent-to-treat patients					
	Metronidazole lotion		Vehicle		p value
	# pts	Mean	# pts	Mean	
Week 3	71	- 30.3	68	- 10.3	0.009
Week 6	66	- 46.4	64	- 16.8	0.000
Week 9	66	- 56.1	60	- 26.8	0.000
Week 12	65	- 54.9	60	- 20.4	0.000
Endpoint	72	- 50.5	72	- 17.5	0.000

b. Other clinical signs.

The mean scores for erythema and telangiectasis at each evaluation time were as follows.

ERYTHEMA Intent-to-treat patients					
	Metronidazole lotion		Vehicle		p value
	# pts	Mean	# pts	Mean	
Baseline	72	2.4	72	2.3	0.378
Week 3	71	1.9	68	2.1	0.019
Week 6	66	1.7	64	1.9	0.397
Week 9	66	1.4	60	1.6	0.242
Week 12	65	1.5	60	1.7	0.191
Endpoint	72	1.6	72	1.8	0.065

TELANGIECTASIA Intent-to-treat patients					
	Metronidazole lotion		Vehicle		p value
	# pts	Mean	# pts	Mean	
Baseline	72	1.5	72	1.6	0.160
Week 3	71	1.5	68	1.7	0.040
Week 6	66	1.4	64	1.7	0.025
Week 9	66	1.4	60	1.6	0.153
Week 12	65	1.4	60	1.6	0.101
Endpoint	72	1.4	72	1.6	0.047

c. Investigator's global assessment. The global assessment at week 12 and at endpoint were as follows.

INVESTIGATOR'S GLOBAL EVALUATION			
Intent-to-treat patients			
	Metronidazole lotion	Vehicle	p value
Week 12			
Clear	5 (7.7%)	0	0.000
Marked improvement	21 (32.3%)	12 (20%)	
Definite improvement	21 (32.3%)	9 (15%)	
Minimal improvement	7 (10.8%)	14 (23.3%)	
No change	8 (12.3%)	16 (26.7%)	
Worse	3 (4.6%)	9 (15%)	
Endpoint			
Clear	5 (7%)	0	0.000
Marked improvement	21 (29.6%)	12 (17.1%)	
Definite improvement	21 (29.6%)	10 (14.3%)	
Minimal improvement	10 (14.1%)	15 (21.4%)	
No change	9 (12.7%)	23 (32.9%)	
Worse	5 (7%)	10 (14.3%)	

4) Safety evaluation. The incidence and severity of burning, dryness, and pruritus at baseline, and the incidence and maximum severity during treatment for all treated patients were as follows.

BURNING				
	Metro lotion		Vehicle	
	Baseline	Maximum	Baseline	Maximum
None	39 (54%)	37 (52%)	46 (64%)	38 (54%)
Mild	20 (28%)	24 (34%)	14 (19%)	25 (36%)
Moderate	8 (11%)	8 (11%)	6 (8%)	7 (10%)
Severe	5 (7%)	2 (3%)	6 (8%)	0
Total # pts	72	71	72	70

DRYNESS				
	Metro lotion		Vehicle	
	Baseline	Maximum	Baseline	Maximum
None	12 (17%)	33 (47%)	22 (31%)	37 (53%)
Mild	31 (43%)	26 (37%)	17 (24%)	19 (27%)
Moderate	18 (25%)	9 (13%)	21 (29%)	10 (14%)
Severe	11 (15%)	3 (4%)	12 (17%)	4 (6%)
Total # pts	72	71	72	70

PRURITUS				
	Metro lotion		Vehicle	
	Baseline	Maximum	Baseline	Maximum
None	28 (39%)	31 (44%)	40 (56%)	36 (51%)
Mild	26 (36%)	28 (39%)	15 (21%)	21 (30%)
Moderate	15 (21%)	9 (13%)	13 (18%)	13 (19%)
Severe	3 (4%)	3 (4%)	4 (6%)	0
Total # pts	72	71	72	70

Fifteen adverse events which were considered to be possibly, probably, or definitely related to treatment occurred in fourteen patients; these were as follows.

ADVERSE EVENTS Possibly, probably, or definitely related to treatment		
	Metronidazole lotion	Vehicle
Local allergic reaction	2	0
Contact dermatitis	2	0
Skin discomfort	0	1
Erythema	4	0
Dry skin	1	0
Condition worse	1	4

All of the above events were mild to moderate in severity. Six of the patients completed the study, and eight of the patients were discontinued from the study due to the adverse event. Of the patients that continued on the study, one had a moderate irritant contact dermatitis with metronidazole lotion; after interruption of treatment for 5 days, treatment was resumed with no further irritation. Another patient had reported a mild allergic contact dermatitis; after interruption of treatment for 10 days and change in the skin cleanser used, treatment was resumed with no further dermatitis.

Eight patients were discontinued because of adverse events which were considered to be possibly, probably, or definitely related to treatment; this comprised four on metronidazole lotion and four on the vehicle. The four patients on metronidazole lotion are described further as follows.

- Patient metronidazole lotion: discontinued the study after 5 weeks of treatment due to irritant contact dermatitis, with symptoms of increased erythema and fine scaling.
- Patient metronidazole lotion: discontinued the study after 9 weeks of treatment due to worsening of the rosacea.
- Patient metronidazole lotion: discontinued the study after 1 week of treatment due to possible allergic contact dermatitis. The investigator felt that the dermatitis was probably caused by Cetaphil Skin Cleanser, or possibly by the metronidazole lotion. Patch testing was not done. The patient had a history of prior successful use of MetroGel, and no prior use of Cetaphil.

- Patient - metronidazole lotion: discontinued the study after 3 weeks of treatment due to increased facial erythema.

The four patients on the vehicle discontinued due to worsening of the rosacea. In addition three additional vehicle patients discontinued due to worsening of the rosacea; the relationship to treatment was considered by the investigator to be unlikely.

Forty-five patients had hematology and clinical chemistries done at baseline and at week 12. As judged by the investigator and the Medical Monitor, no hematological or clinical chemistry parameter which was out of range was considered to be clinically significant.

Reviewer's comments: In summary, for the efficacy evaluable patients metronidazole lotion 0.75% was significantly superior to the lotion vehicle at week 12 and at endpoint in the mean inflammatory lesion counts, the mean percent reduction in inflammatory lesion counts, and in the investigator's global evaluation. Metronidazole lotion 0.75% was also significantly superior to the vehicle in these parameters in the intent-to-treat population.

In the safety evaluation the incidence and severity of burning, dryness, and pruritus during treatment were somewhat less than at baseline. Other adverse events which were possibly, probably, or definitely related to treatment were a local allergic reaction in 1, irritant contact dermatitis in 2, erythema in 4, dry skin in 1, and worsening of the rosacea. (Another event, reported as a local allergic reaction, was not sensitization to metronidazole lotion.)

Forty-five patients had clinical chemistries and hematological parameters at baseline and at week 12; changes in these values did not appear to be clinically significant.

Labeling review: Review of the sponsor's draft package insert is appended to this medical officer's review.

Summary and Evaluation

MetroLotion (metronidazole) 0.75% is a line extension to the currently marketed MetroCream and MetroGel; the indication is for the treatment of the inflammatory papules and pustules of rosacea.

Cutaneous safety studies which were performed included cumulative irritancy, contact sensitization, phototoxicity, and photosensitization. It is felt that the results of these studies are adequate to demonstrate that the product has little or no potential for elicitation of these reactions.

One pivotal clinical effectiveness study was performed. This was a double blind, multicenter, parallel group comparison of MetroLotion with its vehicle in 125 evaluable patients with moderate to severe rosacea, using a treatment regimen of applications BID for 12 weeks. The primary efficacy parameters were inflammatory lesion counts and an investigator's global assessment of improvement. The results showed a significant superiority of MetroLotion over the vehicle at week 12 and at endpoint in the mean inflammatory lesion counts, the mean percent reduction in inflammatory lesion counts, and in the investigator's global evaluation.

The safety evaluation showed a somewhat lesser incidence and severity of burning, dryness, and pruritus during treatment than at baseline. Adverse events included a possible sensitization reaction, and several irritant reactions of mild to moderate severity.

Conclusions: *It is felt that these studies adequately demonstrate the safety and effectiveness of MetroLotion in the treatment of the inflammatory papules and pustules of rosacea.*

Recommendations: *With the specified labeling revisions, it is recommended that this NDA be approved for the use of MetroLotion in the treatment of the inflammatory papules and pustules of rosacea, when applied twice daily for 12 weeks.*

Cc: Orig NDA

HFD-540/Division File

HFD-540/Huene

HFD-540/Kozminski

HFD-540/DeCamp

HFD-540/Jacobs

HFD-540/WALKER

/S/

M.D.

Phyllis A. Huene, M.D.

S. L. 10/27/98

420 11/5/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-901

CHEMISTRY REVIEW(S)

NOV 16 1998

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-901 CHEM. REVIEW #: 02 REVIEW DATE: 22-SEP-98

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	28-NOV-97	02-DEC-97	12-DEC-97
BC	10-JUN-98	11-JUN-98	11-JUN-98
BL	10-JUL-98	13-JUL-98	13-JUL-98
BC	17-AUG-98	18-JUL-98	18-JUL-98
BC	15-SEP-98	16-SEP-98	17-SEP-98
BL	02-OCT-98	05-OCT-98	06-OCT-98

NAME & ADDRESS OF APPLICANT:

Galderma Laboratories, Inc.
3000 Alta Mesa Blvd
Suite 300
Fort Worth, Texas 76163

DRUG PRODUCT NAME:

Proprietary:

MetroLotion

Nonproprietary/USAN:

Metronidazole

Code Names:

Chemical Type/

Therapeutic Class:

3,S

PHARMACOLOGICAL INDICATION:

topical treatment of rosacea

DOSAGE FORM:

Lotion

STRENGTHS:

0.75% (7.5 mg/g)

ROUTE OF ADMINISTRATION:

Topical

DISPENSED:

Rx OTC

SPOTS:

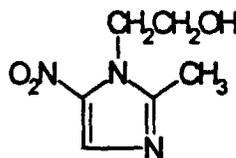
YES NO

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:

2-Methyl-5-nitroimidazole-1-ethanol

Molecular weight: 171 g/mol

CAS # 443-48-1



SUPPORTING DOCUMENTS: Chemistry review #1, dated 9 April-98

REMARKS/COMMENTS:

Metronidazole, formulated at 0.75% in a lotion, is the third dosage form of metronidazole to be sponsored by Galderma Laboratories, Inc. MetroGel® and MetroCream™ were approved on November 22, 1988 and September 20, 1995, respectively.

MetroLotion (metronidazole) Topical Lotion, 0.75%
Galderma Laboratories

All three dosage forms are indicated for twice daily application in the treatment of rosacea.

Metronidazole is a compendial drug substance. DMFs and letters of authorization were included for the drug substance and packaging components. The Office of Compliance issued an acceptable recommendation to the drug substance manufacturer on January 8, 1998. The requested trademark was deemed acceptable on March 1, 1998.

This NDA was recommended as approvable by the original chemistry reviewer, J. Higgins. However, it was further recommended that an information request letter be issued to the applicant in order to resolve certain technical points. Moreover, it was also recommended that the response(s) to the information request letter be approved before final approval of the chemistry portion of the NDA.

The purpose of this review is to respond to the information request letter, dated 24 April 1998, and to review recently submitted stability data and draft labeling.

CONCLUSIONS & RECOMMENDATIONS:

The subject application is APPROVED under section 505 of the FFD&C Act.

TS/

William C. Timmer, Ph.D.
Review Chemist

cc: Orig. NDA 20-901
HFD-540/Division File
HFD-540/Division Director/JWilkin
HFD-540/MO/BVaughan
HFD-540/PharmTox/JAvalos
HFD-540/PM/MWright
HFD-540/Biopharm/VTandon
HFD-540/Biostat/VFreidlin
HFD-160/Micro/CVincent
HFD-540/Chemist/WTimmer
HFD-540/ChemistTL/WHDeCamp

11/16/98

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Kummerer
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APR 24 1998

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls-

NDA #: 20-901 CHEM.REVIEW #: 01 REVIEW DATE: 09-APR-98

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	28-NOV-97	02-DEC-97	12-DEC-97

NAME & ADDRESS OF APPLICANT: Galderma Laboratories, Inc.
3000 Alta Mesa Blvd, Suite 300
Fort Worth, Texas 76163

DRUG PRODUCT NAME

<u>Proprietary:</u>	MetroLotion
<u>Nonproprietary/USAN:</u>	Metronidazole
<u>Code Names/ #'s:</u>	
<u>Chemical Type/</u>	
<u>Therapeutic Class:</u>	3S

PHARMACOLOGICAL CATEGORY/INDICATION: for topical application
in the treatment of rosacea

<u>DOSAGE FORM:</u>	Lotion
<u>STRENGTHS:</u>	0.75% (7.5 mg/g)
<u>ROUTE OF ADMINISTRATION:</u>	Topical
<u>DISPENSED:</u>	<u>XXX</u> Rx <u> </u> OTC
<u>SPOTS:</u>	<u> </u> YES <u>XX</u> NO

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:

Metronidazole (refer to USP/USAN)

2-Methyl-5-nitroimidazole-1-ethanol

CAS # 443-48-1

SUPPORTING DOCUMENTS:

Document Type & Number	Subject	Holder	Status	Review Date	Letter Date
IND	Metronidazole Topical Gel, 0.75%	Galderma Laboratories, Inc.	ACTIVE	3-25-85 11-14-90 10-3-91	N/A
IND	Metronidazole Topical Cream, 0.75%	Galderma Laboratories, Inc.	ACTIVE	12-21-93	N/A
IND	Metronidazole Topical Lotion, 0.75%	Galderma Laboratories, Inc.	ACTIVE	10-25-94 4-21-95 12-12-94	N/A
NDA 19-737	MetroGel (Metronidazole) Topical Gel, 0.75%	Galderma Laboratories, Inc.	AP	8-1-88 8-16-88	11-22-88
NDA 20-531	MetroCream (Metronidazole) Topical Cream, 0.75%	Galderma Laboratories, Inc.	AP	6-10-95 7-6-95 8-15-95	9-20-95
DMF	Metronidazole USP drug substance manufacture and controls		IA IA IA A A	12-12-91 10-25-94 4-8-96 9-9-96 4-9-98	12-12-91 12-9-94 4-9-96
DMF	Organization and facilities		OPEN	N/A	N/A
DMF	resin		A A A A	2-21-96 12-27-96 7-30-97 12-4-97	
DMF	blow molding process for PE bottles		IA A A	8-4-93 9-3-93 4-2-98	8-9-93
DMF			IA IA IA A	8-25-93 5-31-94 12-12-96 6-24-96	8-26-93 5-31-94 6-2-94 2-13-96

REMARKS/COMMENTS:

Metronidazole formulated at 0.75% in a lotion dosage form is the third dosage form of metronidazole to be sponsored by Galderma Laboratories, Inc. MetroGel and MetroCream were approved on November 22, 1988 and September 20, 1995, respectively. All three dosage forms are indicated for twice daily application in the treatment of rosacea.

Metronidazole is a compendial drug substance. DMFs and letters of authorization have been provided for the drug substance and packaging components. The applicant has included a statement which reveals their readiness for inspection.

The establishment request was transferred to the Office of Compliance on December 31, 1997. The Office of compliance issued an acceptable recommendation on January 8, 1998.

A trademark consult was requested on January 2, 1998 and an acceptable recommendation was received on March 1, 1998.

CONCLUSIONS & RECOMMENDATIONS:

The subject application is approvable. It is this reviewer's recommendation that an information request letter be issued to advise the applicant of information that would be required for an approval recommendation from chemistry.

IS/

4/15/98

Janet G. Higgins
Review Chemist

cc: Orig. NDA 20-901
HFD-540/Division File
HFD-540/Higgins/
HFD-540/MO/Vaughan
HFD-540/Pharm/Avalos
HFD-540/CSO/Kummerer
HFD-540/BIOPHARM/Tandon
HFD-540/BIOSTAT/Freidlin
HFD-520/MICRO/Vincent
HFD-540/SUPERVISOR/De Camp *4/24/98*
R/D Init by: SUPERVISOR

filename: N20901.org

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-901

PHARMACOLOGY REVIEW(S)

HFD 540/kumma

**Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products (HFD-540)**

MAR 24 1998

NDA 20-901 (000)

Date Submitted: November 28, 1997

Number of Volumes: 19

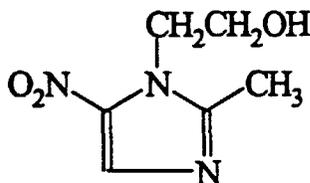
Date CDER Received: December 2, 1997

Date Assigned: December 12, 1997

Drug: Metronidazole 0.75% lotion (MetroLotion™)

Chemical Name: 2-methyl-5-nitro-1H-imidazole-1-ethanol

Chemical Structure:



Molecular Weight: 171.16

Molecular Formula: C₆H₉N₃O₃

Category: Antibacterial and antiprotozoal agent

**Sponsor: Galderma Laboratories, Inc.
3000 Alta Mesa Blvd., Suite 300
Forth Worth, Texas 76133
(817) 263-2676**

Indication: For the treatment of rosacea

Route of Administration: Topical

Submissions Cross-referenced:

DMF	DMF	DMF	DMF
IND	NDA 19-737 (Metrogel [®])		
IND	NDA 20-531 (MetroCream [™])		
IND	(MetroLotion [™])		

Composition:

<u>Ingredient</u>	<u>per gram</u>	<u>percent (w/w%)</u>
✓ metronidazole, USP	7.5 mg	0.75
✓ carbomer 941, NF	mg	
✓ polyethylene glycol, 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	
✓ glycerin, USP	mg	
✓ potassium sorbate, NF	mg	
✓ lactic acid, USP and/or		
✓ sodium hydroxide, NF		
✓ purified water, USP		1%

Background: Metronidazole in a cream (NDA 20-531) and gel (NDA 19-737) formulation is approved for the treatment of rosacea. Galderma received approval for marketing of MetroGel on November 22, 1988 and MetroCream on September 20, 1995. The development of lotion formulation has involved several meetings and correspondences with the Sponsor. In summary, the Sponsor has fulfilled the non-clinical recommendations made during the development of this product. The current submission contains the studies recommended by the Agency and an updated review of the available pre-clinical scientific data from published literature.

Index of Studies:

A. Pharmacology (Literature submitted IND and NDA 20-531 by the Sponsor)

1. Akamatsu J, Oguchi M, Nishijima S, Asada Y, Takahashi M, Ushijima T, Niwa Y. The inhibition of free radical generation by human neutrophils through the synergistic effects of metronidazole with palmitoleic acid: a possible mechanism of action of metronidazole in rosacea and acne. *Arch. Dermatol Res* 1990; 282: 449-454.
2. Bahr V, and Ullmann U. The influence of metronidazole and its two main metabolites on murine *in vitro* lymphocyte transformation. *Eur J Clin Microbiol* 1983; 2: 568-570.
3. Gnarpe H, Belsheim J, and Persson S. Influence of nitroimidazole derivatives on leukocyte migration. *Scand J Infect Dis (Suppl)* 1981; 26: 68-71.

4. Grove DI, Makmoud AAF, and Warren KS. Suppression of cell-mediated immunity by metronidazole. *Int Archs Allergy Appl Immunol* 1977; 54: 422-427.
5. Marks R. The problem of rosacea. *Br Med J (Clin Res)* 1976; 1:94.
6. Miyachi Y, Imamura S, and Niwa Y. Anti-oxidant action of metronidazole: a possible mechanism of action in rosacea. *Br J Dermatol* 1986; 114: 321-324.
7. Saxena A, Chugh S, and Vinayak VK. Modulation of host immune responses by metronidazole. *Ind J Med Res* 1985; 81: 387-390.
8. Tanga MR, Antani JA, and Kabade SS. Clinical evaluation of metronidazole as an anti-inflammatory agent. *Int Surg* 1975; 60: 75-76.
9. Taylor JAT. Pharmacodynamic observations on metronidazole therapy. Side effects in endocrine, metabolic and auto-immune disorders. III Anti-ischemic and anti-inflammatory action in peripheral vascular disorders. *Proc West Pharmacol Soc* 1966; 9: 37-39.
10. Ursing B and Kamme C. Metronidazole for Crohn's disease. *Lancet (I)* 1975; 775-777.

B. Acute Toxicology (Studies submitted by the Sponsor and previously reviewed)

1. Acute oral toxicity study of 0.75% metronidazole gel in rats.
(Submitted in NDA 19-737)

(Literature submitted by the Sponsor)

2. Bost, RG. Metronidazole: Toxicology and teratology. In Finegold SM, McFadzean JA, Roe FJC, editors. Metronidazole - Proceedings of the International Metronidazole Conference. Montreal, Quebec, Canada. Princeton, NJ:Excerpta Medica 1977a: 112-118.
3. Roe, FJC. Toxicologic evaluation of metronidazole with particular reference to carcinogenic, mutagenic and teratogenic potential. *Surgery* 1983; 93:158-164.
4. Benazet F, Cosar CH, Ganter P, Julou L, Populaire P, and Guillaume L. Activite sur *Trichomonas vaginalis* et autres proprietes chimiotherapeutiques de 1'-(hydroxy-2-ethyl)-I carbamoyl-2-nitro-5-pyrrole (15.960 R.P.). *Comptes Rendus Acad Sci* 1966; 263: 609.

C. Multiple Toxicity Studies (Studies submitted by the Sponsor and previously reviewed)

1. Subchronic (4 weeks) toxicity study by the cutaneous route in Sprague Dawley strain of rat of Rozex lotion and Rozex gel containing metronidazole at 0.75%. Pharmacokon Europe, Report Number 1.CG.03.SRE.8163 (submitted in IND and NDA 19-737)
2. 13-Week cutaneous route toxicity study of 0.75% metronidazole gel in rabbits.
(Submitted in NDA 19-737)

(Literature submitted by the Sponsor)

3. Bost, RG. Metronidazole: Toxicology and teratology. In Finegold SM, McFadzean JA, Roe FJC, editors. Metronidazole - Proceedings of the International Metronidazole Conference. Montreal, Quebec, Canada. Princeton, NJ:Excerpta Medica 1977a: 112-118.
4. Bradley WG, Karlsson IJ, and Rassol CG. Metronidazole neuropathy. *Br Med J* 1977; 610-611.
5. Eakins MN, Conroy PJ, Searle AJ, Slater TF, and Willson RL. Metronidazole (Flagyl) a radiosensitizer of possible clinical use in cancer chemotherapy: some biochemical and pharmacological considerations. *Biochem Pharmacol* 1976; 25: 1151-1156.
7. McClain RM, Downing JC, and Edcomb JE. Effect of metronidazole on fertility and testicular function in male rats. *Fundamental and Applied Toxicology* 1989; 12:386-389.
8. Scharer K. Selective alterations of Purkinje cells in the dog after oral administration of high doses of nitroimidazole derivatives. *Verh Dtsch Ges Path* 1972; 56: 407-410.

D. Carcinogenicity Studies (Literature submitted by the Sponsor and previously reviewed)

1. Cavaliere A, Bacci M, Amorosi A, Del Gaudio M, and Vitali R. Induction of lung tumors and lymphomas in BALB/c mice by metronidazole. *Tumori* 1983; 69: 379-382.
2. Cavaliere A, Bacci M, and Vitali R. Induction of mammary tumors with metronidazole in female Sprague-Dawley rats. *Tumori* 1984; 70: 307-311.

3. Chacko M and Bhide SV. Carcinogenicity, perinatal carcinogenicity, and teratogenicity of low dose metronidazole (MNZ) in Swiss mice. *J Cancer Res Clin Oncol* 1986; 112: 135-140.
4. Cohen SM, Erturk E, Von Esch AM, Crovetti AJ, and Bryan GT. Carcinogenicity of 5-nitrofurans, 5-nitroimidazoles, 4-nitrobenzenes, and related compounds. *JNCI* 1973; 51: 403-417.
5. Rust JH. An assessment in the tumorigenicity studies in the mouse and rat. In Finegold SM, McFadzean JA, Roe FJC, editors. Metronidazole - Proceedings of the International Metronidazole Conference. Montreal, Quebec, Canada. Princeton, NJ:Excerpta Medica 1977: 138-144.
6. Rustia M and Shubik P. Induction of lung tumors and malignant lymphomas in mice by metronidazole. *JNCI* 1972; 48: 721-729.
7. Rustia M and Shubik P. Experimental induction of hepatomas mammary tumors, and other tumors with metronidazole in non-inbred Sas:MRC(WI)BR rats. *JNCI* 1979; 63: 863-868.
8. Rustia M, Shubik P, Patil K, and Clayson D. Multiple tumor types induced with the trichomonacide drug Flagyl in rats. In Proceedings of the Seventh Annual Meeting of the American Association for Cancer Research 1979; 20:abstract 216.
9. Roe JFC. Metronidazole: tumorigenicity studies in mice, rats, and hamsters. In Finegold SM, McFadzean JA, Roe FJC, editors. Metronidazole - Proceedings of the International Metronidazole Conference. Montreal, Quebec, Canada. Princeton, NJ:Excerpta Medica 1977: 132-137.

(Literature studies not previously reviewed)

10. Kelly, GE, Meile WD, and Moore, DE. Enhancement of UV-induced skin carcinogenesis by azathioprine: role of photochemical sensitization. *Photochem and Photobiol.* 1989;49(1):59-65.

E. Mutagenicity Studies (Literature submitted by the Sponsor and previously reviewed)

1. Andersen M, Binderup ML, Keil P, and Larsen H. Mutagenicity of metronidazole. *Arch Pharm Chemi Sci Ed* 1982; 10: 25-44 (and references within).
2. Bost, RG. Metronidazole: mammalian mutagenicity. In Finegold SM, McFadzean JA, Roe FJC, editors. Metronidazole - Proceedings of the International Metronidazole Conference. Montreal, Quebec, Canada. Princeton, NJ:Excerpta Medica 1977b: 126-131.

3. Cantelli-Forti G, Aicardi G, Guerra MC, Barbara AM, and Biagi GL. Mutagenicity of a series of 25 nitroimidazoles and two nitrothiazoles in *Salmonella typhimurium*. *Teratogenesis Carcinogen, Mutagen* 1983; 3:51-63.
4. Connor TH, Stoeckel M, Evrard J, and Legator MS. The contribution of metronidazole and two metabolites to the mutagenic activity detected in urine of treated humans and mice. *Cancer Res* 1977; 37: 629-633.
5. Dayan J, Crajer MC, and Deguingand S. Mutagenic activity of 4 active-principle forms of pharmaceutical drugs: Comparative study in the *Salmonella typhimurium* microsome test, and the HGPRT and Na⁺/K⁺ ATPase systems in cultured mammalian cells. *Mutat Res* 1982; 102: 1-12.
6. Dunlop JR, Mahood JS, and Willson RL. Metronidazole and misonidazole: absence of cytogenetic effects in a euoxic bacterial and mammalian cell system *in vitro*. In Breccia A, Cavalleri B, and Adams GE (eds), Nitroimidazoles: Chemistry, Pharmacology, and Clinical Application 1982; 40: 171-181.
7. Edwards DI. The action of metronidazole on DNA. *J Antimicrob Chemother* 1977; 3: 43-48.
8. Edwards DI. Mechanism of cytotoxicity of nitroimidazole drugs. *Prog Med Chem* 1981; 18: 87-116.
9. Geard CR, Schwarts LE, and Rutledge-Freeman MH. Clastogenic effect of misonidazole on aerated and hypoxic cells. In Brady LW, ed, Radiation Sensitizers: Their Use in the Clinical Management of Cancer. New York: Masson Publishing USA, Inc.; 1981:460-465.
10. Hartley-Asp B. Metronidazole exhibits no cytogenetic effect in the micronucleus test in mice or in human lymphocytes *in vitro*. *Mutat Res* 1979; 67: 193-196.
12. Korbelik M and Horvat D. The mutagenicity of nitroaromatic drugs - effect of metronidazole after incubation in hypoxia *in vitro*. *Mutat Res* 1980; 78: 201-207.
13. Kramers PG. Mutagenicity of nitro compounds in *Drosophila melanogaster*. *Mutat Res* 1978; 53: 213.
14. Lambert BA, Lindblad A, and Ringborg U. Absence of genotoxic effect of metronidazole and two of its urinary metabolites on human lymphocytes *in vitro*. *Mutat Res* 1979;

67:281-287.

15. LaRusso NF, Tomaz M, Kaplan D, and Muller M. Absence of strand breaks in deoxyribonucleic acid treated with metronidazole. *Antimicrob Agents Chemother* 1978; 13: 19-24.
16. Legator MS, Connor TH, and Stoeckel M. Detection of mutagenic activity of metronidazole and nitridazole in body fluids of humans and mice. *Science* 1975; 188: 1118-1119.
17. Lindmark DG and Muller M. Antitrichomonad action, mutagenicity, and reduction of metronidazole and other nitroimidazoles. *Antimicrob Agents Chemother* 1976; 10: 476-482.
18. Mahood JS and Willson RL. Failure to induce sister chromatid exchange (SCE) with metronidazole. *Toxicol Lett* 1981; 8: 359-361.
19. Mahood JS and Willson RL. Metronidazole (Flagyl): lack of induction of sister chromatid exchanges in CHO-K1 cells. *Mutat Res* 1983; 122:187-192.
20. McCalla DR, Voustinos D, and Olive PL. Mutagen screening with bacteria: niridazole and nitrofurans. *Mutat Res* 1975; 31: 31-37.
22. Mohn GR, Ong T-M, Callen DF, Kramers PGN, and Aaron CS. Comparison of the genetic activity of 5-nitroimidazole derivatives in *Escherichia coli*, *Neurospora crassa*, *Saccharomyces cerevisiae*, and *Drosophila melanogaster*. *J Environ Pathol Toxicol* 1979; 2: 657-670.
23. Mohtashampur E and Norpoth K. Excretion of mutagens in sweat and feces of man, and in serum, gastric juice and urine of rats, after oral dosing of niridazole or metronidazole. *Mutagenesis* 1986; 1: 371-374.
24. Molina L, Rinkus S, and Legator MS. Evaluation of the micronucleus procedure over a 2-year period. *Mutat Res* 1978; 53: 125.
25. Mudry MD, Carballo M, Labal de Vinuesa M, Gonzalez Cid M, and Larripa I. Mutagenic bioassay of certain pharmacological drugs: II. Metronidazole (MTZ). *Mutat Res* 1994; 305: 127-132.
26. Neal SB and Probst GS. Chemically-induced sister-chromatid exchange *in vivo* in bone

marrow of Chinese hamster. *Mutat Res* 1983; 113: 33-43.

27. Olive PL. Correlation between the half-wave reduction potentials of nitroheterocycles and their mutagenicity in Chinese hamster V79 spheroids. *Mutat Res* 1981; 82: 137-145.
28. Olive PL and McCalla DR. Damage to mammalian cell DNA by nitrofurans. *Cancer Res* 1975; 35: 781-784.
29. Ong T-M, Slade B, and de Serres FJ. Mutagenicity and mutagenic specificity of metronidazole and niridazole in *Neurospora crassa*. *J of Environ Pathol Toxicol* 1978; 2: 1109-1118.
30. Probst GS, McMahon RE, Hill LE, Thompson CZ, Epp JK, and Neal SB. Chemically-induced unscheduled DNA synthesis in primary rat hepatocytes cultures: a comparison with bacterial mutagenicity using 218 compounds. *Environ Mutagen* 1981; 3: 11-32.
31. Prosser JS and Hesketh LC. Hypoxic cell sensitizers and sister chromatid exchanges. *Br J Radiol* 1980; 53: 376-377.
32. Prosser JS and White CM. Flagyl and radiation-induced chromosome breakage. *Br J Dermatol* 1976; 51: 654-655.
33. Roe, FJC. Toxicologic evaluation of metronidazole with particular reference to carcinogenic, mutagenic and teratogenic potential. *Surgery* 1983; 93:158-164.
34. Rosenkranz HS and Speck WT. Mutagenicity of metronidazole: activation by mammalian liver microsomes. *Biochem Biophys Res Commun* 1975; 66:520-525.
35. Sina JF, Bean CL, Dysart GR, Taylor VI, and Bradley MO. Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/ mutagenic potential. *Mutat Res* 1983; 113:357-391.
36. Speck WT, Stein AB, and Rosenkranz HS. Mutagenicity of metronidazole: presence of several active metabolites in human urine. *JNCI* 1976; 56:283-284.
37. Sutherland RM. Selective chemotherapy of non-cycling cells in an *in vitro* tumor model. *Cancer Res* 1974; 39:50.
38. Trzos RJ, Petzold GL, Brunden MN, and Swenberg JA. The evaluation of sixteen carcinogens in the rat using the micronucleus test. *Mutat Res* 1978; 56:79-86.
39. Varghese AJ, Gulyos S, and Mohindra JK. Hypoxia dependent reduction of 1-(2-nitro-

1-imidazolyl)-3-methoxy-2-propanol by Chinese hamster ovary cells and KHT tumor cells *in vitro* and *in vivo*. *Cancer Res* 1976; 36:3761-3765.

40. Voogd CE. On the mutagenicity of nitroimidazoles. *Mutat Res* 1981; 86:243-277.
41. Voogd CE, van der Stel JJ, and Jacobs JA. The mutagenic action of nitroimidazoles, metronidazole, nimorazole, dimetridazole and ronidazole. *Mutat Res* 1974; 26:483-490.
42. Voogd CE, van der Stel JJ, and Jacobs JA. The mutagenic action of nitroimidazoles, IV: A comparison of the mutagenic action of several nitroimidazoles and some imidazole. *Mutat Res* 1979; 66:207-221.
43. Willson RL. In Finegold SM, McFadzean JA, Roe FJC, editors. Metronidazole - Proceedings of the International Metronidazole Conference. Montreal, Quebec, Canada. Princeton, NJ:Excerpta Medica 1977: 147-175.

E. Reproduction Studies (Literature submitted by the Sponsor and previously reviewed)

1. Bost, RG. Metronidazole: Toxicology and teratology. In Finegold SM, McFadzean JA, Roe FJC, editors. Metronidazole - Proceedings of the International Metronidazole Conference. Montreal, Quebec, Canada. Princeton, NJ:Excerpta Medica 1977a: 112-118.
2. Cella PL. Experimental studies on the teratology of metronidazole. *Rivista di Patologia e Clinica* 1969; 24: 529-537.
3. Chacko M and Bhide SV. Carcinogenicity, perinatal carcinogenicity, and teratogenicity of low dose metronidazole (MNZ) in Swiss mice. *J Cancer Res Clin Oncol* 1986; 112: 135-140.
4. Damjanov I. Metronidazole and alcohol in pregnancy. *JAMA* 1986; 256: 472.
5. Giknis MLA and Damjanov I. The transplacental effects of ethanol and metronidazole in Swiss-Webster mice. *Toxicol Lett* 1983; 19:37-42.
6. Ivanov I. The effect of "trichomonacid" on pregnancy in experimental animals. *Akush Ginekl (Sofia)* 1969; 8:241-244.
7. Roe, FJC. Toxicologic evaluation of metronidazole with particular reference to carcinogenic, mutagenic and teratogenic potential. *Surgery* 1983; 93:158-164.

8. Takakubo F, Ibrahim E, and Eto K. Teratogenic effects of metronidazole on cultured rat embryos. *Teratol* 1986; 3413: 453-454.

G. Special Toxicity Studies (Study submitted by the Sponsor and previously reviewed)

H. Absorption, Distribution, Metabolism, and Excretion Studies (Reports were performed by Sponsor at Galderma CIRD, France)

1. *In vitro* study with metronidazole topical gel 0.75% and metronidazole topical cream 0.75%. Galderma CIRD, Valbonne, France. Report Number 1.CG.03.SRE.4516.INF.
2. *In vitro* study with metronidazole topical gel 0.75% and metronidazole topical lotion 0.75%. Galderma CIRD, Valbonne, France. Report Number 1.CG.03.SRE.4521.INF.

(Literature submitted by the Sponsor)

3. Aronson IK, Rumsfield JA, West DP, Alexander J, Fischer JH, and Paloucek FP. Evaluation of topical metronidazole gel in acne rosacea. *Drug Intell Clin Pharm* 1987; 21:346-351.
4. Brogden RN, Heel RC, Speight TM, and Avery GS. Metronidazole in anaerobic infections: a review of its activity, pharmacokinetics and therapeutic use. *Drugs* 1978; 16:387.
5. Buttar HS. Fate of metronidazole following intravaginal and intravenous administration to rabbits. *J Toxicol Environ Health* 1982; 9:305-316.
6. Buttar HS and Siddiqui WH. Pharmacokinetics and metabolic disposition of ¹⁴C-metronidazole-derived radioactivity in rat after intravenous and intravaginal administration. *Arch Int Pharmacodyn Ther* 1980, 245:4-19.

7. Buttar HS, Siddiqui WH, and Moffatt JH. The disposition of ¹⁴C-metronidazole in rats following vaginal and oral administration. *J Pharm Pharmacol* 1979; 31:542-544.
8. Eakins MN, Conroy PJ, Searle AJ, Slater TF, and Willson RL. Metronidazole (Flagyl) a radiosensitizer of possible clinical use in cancer chemotherapy: some biochemical and pharmacological considerations. *Biochem Pharmacol* 1976; 25: 1151-1156.
9. Holter O, Bergan T, Florenes T, and Leinebo O. Penetration of metronidazole to tissues. *J Antimicrob Chemother* 1983; 11:357.
10. Hospador MA and Manthei RW. Influence of age and diet on the induction of hexobarbital-metabolizing enzymes in the mouse. *Proc Soc Exp Biol Med* 1968; 128:130-12.
11. Ings RMJ, Law GL, and Parnell EW. The metabolism of metronidazole (1-(2'-hydroxyethyl-2-methyl-5-nitroimidazole). *Biochem Pharmacol* 1966; 15:515-519.
12. Ings RMJ, McFadzean JA, and Ormerod WE. The fate of metronidazole and its implications in chemotherapy. *Xenobiotica* 1975; 5:223-235.
13. Iyer KS and Kutty AG. Influence of metronidazole and chloral hydrate on the activity of other drugs. *Indian J Physiol Pharmacol* 1974; 18:49-52.
14. Kling PA and Burman LG. Serum and tissue pharmacokinetics of intravenous metronidazole in surgical patients. *Acta Chir Scand* 1989; 155:347.
15. Lau AH, Lam NP, Pistelli SC, Wilkes L, and Danziger LH. Clinical pharmacokinetics of metronidazole and other nitroimidazole anti-infectives. *Clin Pharmacokineti* 1992; 23:328.
16. Ludwig E, Csiba A, Magyar T, Szocs G, and Graber H. Age-associated pharmacokinetics changes of metronidazole. *Int J Clin Pharmacol Ther Toxicol* 1983; 21:87.
17. Meszaros C and Szporny L. Urinary excretion of metronidazole and isometronidazole in the rat. *Acta Physiol Hung* 1968; 34:103-106.
18. Passmore CM, McElnay JC, Rainey EA, and D'Arcy PF. Metronidazole excretion in human milk and its effects on the suckling neonate. *Br J Clin Pharma* 1988; 26:45.
19. Placidi GF, Masuoka D, Clearaz A, Taylor JAT, and Earle R. Distribution and metabolism of ¹⁴C-metronidazole in mice. *Arch Int Pharmacodyn Ther* 1970; 188:168-179.

20. Stambaugh JE, Feo LG, and Manthei RW. The isolation and identification of the urinary oxidative metabolites of metronidazole in man. *J Pharmacol Exp Ther* 1968; 161:373-381.
21. Templeton R. In Finegold SM, McFadzean JA, Roe FJC, editors. Metronidazole - Proceedings of the International Metronidazole Conference, Montreal, Quebec, Canada. Princeton, NJ:Excerpta Medica 1977:28-49.

Preclinical Studies

Pharmacology

The pharmacology of metronidazole is summarized.

Metronidazole is a broad spectrum antiparasitic and antimicrobial agent. This compound is clinically effective in trichomoniasis, amebiasis, and giardiasis. Several reports have implicated metronidazole of having direct anti-inflammatory effects, and effects on neutrophil motility, lymphocyte transformation, and some aspects of cell-mediated immunity (Akamatsu *et al.*, 1990; Miyachi *et al.*, 1986; Marks, 1976; Taylor, 1966; Gnarpe *et al.*, 1981; Bahr and Ullman, 1983; Tanga *et al.*, 1975; Grove *et al.*, 1977; Saxena *et al.*, 1985; Ursing and Kamme, 1975). Metronidazole can significantly reduce the levels of hydrogen peroxide and hydroxyl radicals produced *in vitro* by zymosan-stimulated neutrophils (Miyachi *et al.*, 1986). The generation of reactive oxygen species by neutrophils and in the xanthine-xanthine oxidase system increased in a dose dependent and synergistic manner in the presence of the skin free fatty acid, palmitoleic acid (Akamatsu *et al.*, 1990). Metronidazole has demonstrated some efficacy against anaerobic bacteria and protozoa, but not against aerobes. The antimicrobial properties of metronidazole were also demonstrated with the combination of metronidazole and palmitoleic acid. The incorporation of either 100 ug/ml metronidazole alone or 1 ug/ml palmitoleic acid alone to *P. acnes* cultures lead to bacterial levels of 2.0×10^7 and 2.0×10^8 colony forming units, respectively. However, the combination of these two products at these respective concentrations markedly decreased the bacterial level to 1.4×10^4 colony forming units. *In vivo*, metronidazole was able to reduce inflammatory lesions and erythema in rosacea patients.

Overall, the mechanism by which metronidazole ameliorates the lesions and erythema of rosacea is not known. Based on the experimental and clinical data, the mechanism may be related to the anti-inflammatory or immunosuppressive actions of the drug and maybe even the suppression of skin bacteria.

Toxicology

The acute and chronic toxicity of metronidazole have been evaluated and the results are summarized. The toxicity of metronidazole has been examined in five species: dog, rat, mice, rabbit, and monkey (most strains were not specified). The acute toxicity (LD₅₀) of metronidazole

to mice and rats is in the range of 1-5 g/kg depending on the route of administration (Roe, 1983; Bost, 1977a). An oral administration of 0.75% metronidazole in a gel formulation to Sprague-Dawley rats did not reveal any clinical signs of toxicity with doses of 5 g of cream/kg (Report Number 60706397). The subchronic study performed by the Sponsor found that a 13-week, 24 hour exposure, topical administration of metronidazole (0.75%) in a gel did not produce any drug-related dermal physical, behavioral, clinical chemistry and hematological, or histopathological changes in the organs of the New Zealand White rabbit.

In the comparative 4-week dermal toxicity study, topical administrations of metronidazole (0.75%) in a gel (Rozex Gel) or lotion (Rozex Lotion) formulation did not cause dermal irritation, deaths or changes in body weights, food consumption, or gross pathology. Components and concentrations of components of the formulations were not described. Liver weights were statistically significantly increased (20%) in female animals treated with the gel. Although statistically significant changes (decreases) were reported in alkaline phosphatase, aspartate amino-transferase, and triglyceride blood levels, the changes were not of toxicological significance. Other statistically significant changes observed in both formulations were decreased white blood cell counts (60%) in female rats, and decreased potassium (15%) and elevated sodium (1%) blood levels in male rats. In the liver of female rats, some foci of extramedullary hematopoiesis were seen in one control, two animals treated with Rozex lotion, and three animals treated with Rozex gel. The only findings associated with treatment of metronidazole was leukopenia. The other findings reported (increased liver weights, extramedullary hematopoiesis, and decreased potassium) could not be directly attributed to the treatment of metronidazole. A more adequate study would better establish the association of these changes with treatment. No other long-term dermal studies were conducted with either metronidazole in a gel, cream, or lotion formulation.

Long-term oral studies have been performed in four species. The dog proved to be the most sensitive species (Scharer, 1972). At a dose of 250 mg/kg/day, a spasmodic state, loss of weight, and eventual death with Purkinje cell degeneration were observed in dogs given four to six doses. At a reduced dose of 150 mg/kg/day, one of two dogs treated had convulsive episodes at 4 weeks. In a second study (Bost, 1977a), an oral dose of 75 mg/kg/day (length of study was not specified) resulted in ataxia, muscular rigidity, and tremors. A lower dose of 50 mg/kg/day did not have any clinical symptoms.

In CF1 and ICR mice, metronidazole was administered at 75, 150, and 600 mg/kg/day in the diet for 92 and 78 weeks, respectively (Bost, 1977a). ICR mice were more sensitive to metronidazole than the CF1 mice. The ICR mice developed testicular atrophy, hypospermatogenesis, decreased seminal vesicles to body weight ratio, and decreased testes to body weight ratio and decreased body weight gains in the high dose males when compared to controls. The female high dose group also had a decreased body weight gain and a decreased uterus to body weight ratio. Body weight gain decreased in all treated groups. In comparison, the body weight gain of the CF1 mice did not differ from control animals. The CF1 mice developed a decreased heart to body weight ratio in female and male animals, and a decreased prostate to body weight ratio in all three male treatment groups. Survival was not affected adversely at any treatment level in either study. In a short-term mammalian assay, an increase in the number of morphologically abnormal mouse spermatozoa was revealed.

A decrease in body weight gain, testis weight, and spermatogenesis were observed in rats receiving oral administrations of metronidazole (300 mg/kg/day) for 18 weeks (Bost, 1977a). Lower doses (150 and 75 mg/kg/day) did not reveal any abnormalities. Intravenous administrations of the same doses to rats for 4 weeks also did not cause remarkable changes. In an 80 week feeding study (Bost, 1977a), rats received doses of 75, 150, 300, and 600 mg/kg/day (the high dose was administered for 13 weeks only). Animals of the high dose groups (300 and 600 mg/kg/day) developed testicular dystrophy, which did not reverse after a 28 week recovery period in the animals of the 300 mg/kg/day group, prostatic atrophy, and decreased body weight gain. The high dose animals had reduced testis weights and the males revealed a reduced spermatogenesis. Reduced spermatogenesis and marked testicular degeneration were also observed in rats receiving dietary concentrations of 400 mg/kg/day for 8 weeks (McClain & Downing, 1986). A lower dose of metronidazole (25 or 100 mg/kg/day) had no adverse effect on spermatozoa (McClain *et al.*, 1989).

In monkeys administered oral doses of 75 and 150 mg/kg/day for 52 weeks, body weight gain was depressed in the treated groups and histological examinations revealed a compound-related effect on the liver in the high dose group (Bost, 1977a). The findings revealed early degenerative changes including hepatocyte size, presence of hypertrophic hepatic nuclei, and presence of multinucleated hepatocytes. Clinical laboratory findings were within normal limits.

In summary, the long-term administration of high doses of metronidazole decreased the rate of weight gain and altered the male reproductive system in mice and rats. Leukopenia was observed in rats treated topically with 15 mg/kg/day for 28 days. In monkeys, long term oral administration caused changes in liver morphology, but no liver function abnormalities were associated with the changes. CNS toxicity was produced in dogs with 75 mg/kg/day metronidazole treatments.

Carcinogenicity Studies

The literature is summarized below:

In regard to the carcinogenicity potential of metronidazole, several studies have been conducted in three species; mouse, rat, and hamster. A significant increase in liver, pituitary, mammary, testicular, and uterual tumors were observed in non-inbred MRC(WI)BR rats given dietary concentrations of 0.06%, 0.3%, or 0.6% (270 mg/kg/day) for 2 years (Rustia & Shubik, 1979). Leydig cell tumor of testes (46.7% vs. 18% in controls) and pituitary adenomas (50% vs. 20% in controls) were observed only in male high dose animals while mammary tumors (76.1% vs. 35.1% in controls) and liver hepatomas (23.3% vs. 0 in controls) were reported in female high dose animals. Only mammary tumors (56.6% and 53.5%) were reported in the other two dose groups (27 and 135 mg/kg/day, respectively). The incidence of these tumors in the two lower doses were found to be not statistically significant. In a second study (Cavaliere *et al.*, 1984) using Sprague Dawley rats, mammary tumors (72% vs. 30% in controls) were observed at 53 weeks with oral gavage administrations of 30 mg/kg/day for 100 days but not in the dietary study (Cohen *et al.*, 1973). A fourth study was conducted in CD albino rats (Rust, 1977). Non significant increases in mammary tumors were reported in the high dose female group (15-17 animals/group). In the latter two studies, Sprague-Dawley rats were given a dietary

concentration of 0.135% (67.5 mg/kg/day) for 66 weeks and CD albino rats were given dietary doses of 75, 150, or 300 mg/kg/day for 80 weeks.

A significant increase in the incidence of lung tumors was observed in male and female CF1 Swiss and male ICR mice given dietary concentrations of 75, 150, and 600 mg/kg/day for 78 or 92 weeks (Rust, 1977). The incidence for the ICR male mice was 33%, 30%, and 50% for low, mid, and high dose groups compared to 12% in controls. The incidence of lung tumors in the male CF1 mice was 25%, 40%, and 68% while in females the incidence was 38%, 48%, and 58% compared to controls (33% and 22%, respectively). Lower dietary doses were not employed in these two studies. Lung adenomas in males and lymphocytic lymphomas in females were noted in BALB/c mice following gavage doses of 66 mg/kg/day for 100 days (Cavaliere *et al.*, 1983). The lung adenomas (66% vs. 26%) were observed beginning at week 52 and the lymphomas (44% vs. 0%) were observed beginning on week 20. Lung tumors were noted in two life-span studies using Swiss mice (Rustia & Shubik, 1972; Cacko & Bhide, 1986). The doses used were 66 mg/kg/day (2 mg/day/5 days) by gavage in the Chacko & Bhide study and dietary concentrations of 0.06%, 0.15%, 0.3%, or 0.5% (75, 187, 375, or 625 mg/kg/day) in the Rustia & Shubik study. Both genders at the 3 highest doses had lung tumors (48-77% vs 18-20% in controls) beginning at week 33 in the Rustia & Shubik study while only female mice had lung tumors at week 24 in the Chacko & Bhide study. The female animals of the two highest doses also had lympho-reticular neoplasms (50% vs. 23%) beginning at week 20 in the former study and liver, spleen, and thymus tumors were also observed in female mice of the latter study. The cumulative incidence of tumors in the latter study was 21% in males and 32% in females treated with metronidazole while the cumulative incidence was 9% and 3% in control animals, respectively. Two life-span carcinogenicity studies in hamsters given dietary concentrations of 0, 30, or 80 mg/kg/day and 0, 0.15%, or 0.3% did not have significant increases in the number of tumors.

Although differences in dose, method of administration, strain of species, and duration of treatments varied among the mouse studies, lung tumors were the predominant neoplastic lesions observed in both genders. The increased incidence of lymphatic neoplasms were only observed in female mice. In rats, the more prominent lesion reported was mammary tumors in two of the four studies conducted. Again, differences in strain of species, method of administration, dose, and duration of treatments existed between the four rat studies. The other lesions reported in rats (one study) were Leydig cell tumor of testes and pituitary adenomas in males and hepatomas in females.

The Sponsor has concluded that the majority of the tumor findings may be irrelevant to humans. According to their analysis of the published rat and mice carcinogenicity studies, technical problems found in their assessment made the findings difficult to interpret. The technical problems cited by the Sponsor were strain of animal used, comparison of tumor findings in older animals treated with test material versus younger control animals, and influence of diet on tumor outcome. Also, the Sponsor is suggesting that high sustained levels of exposure may cause epigenetic mechanisms through hormonal effects, immunosuppression, peroxisome proliferation, and promotion, which may not be physiologically relevant to humans.

In regard to the strain used in these studies, the argument is made that other investigators have found a high spontaneous incidence of mammary tumors in female and pituitary neoplasms

in male and female Charles River CD rats, and a high spontaneous incidence of mammary tumors in female and pituitary tumors in male and female Sprague-Dawley rats. Swiss mice have also been reported to have a high spontaneous incidence of tumors in pulmonary, reticuloendothelial, and lymphatic system.

Although the spontaneous incidence of tumors may be high, the incidence reported in these studies are always compared to the control values. The two rat studies with reported mammary tumors had incidence rates which were 2 times greater than control levels while four of four mouse studies reported with lung tumors had 2-4 fold increases in lung tumor incidence compared to control animals. Furthermore, the incidence of lung tumors was not only reported in the Swiss mouse but also in the BALB/c mouse. Similarly, the incidence of mammary tumors were observed in the two different rat strains (Sprague-Dawley and non-bred Sas:MRC(W1)BR strain).

The Sponsor has also suggested that the higher incidence of prolactinomas (males and females), mammary gland tumors (females), Leydig cell tumors (males) and other tumors may be the result of endocrine disturbances associated with the long term administration of metronidazole. Although other compounds have been shown to cause a greater incidence of endocrine-related tumors due to changes in endocrine homeostasis, metronidazole has not been evaluated for its potential to alter human endocrine homeostasis. As such, the potential of metronidazole to alter endocrine homeostasis may occur in both animals and humans.

The increased incidence of tumors in these studies is also suggested to be the result of metronidazole's effect on gut micro flora. Since metronidazole is microbicidal to the anaerobic component of natural flora, its prolonged administration is believed to have effects on the spectrum of flora in mice and rats, and consequently, on their nutritional status. Body weight decreases were noted in the 78 week mouse study, but no effect was reported in the 98 week study. In addition, enterotoxemia would be of greater concern in the treated animals if metronidazole had a profound effect on gut micro flora. Enterotoxemia was not reported in any study. In fact, the Sponsor found a greater mean survival time in treated animals compared to control animals.

Overall, the long term administration of metronidazole to several species does result in a greater incidence of tumors compared to control animals. More specifically, the administration of metronidazole does lead to an increased incidence of mammary tumors in rats and lung tumors in mice. The Sponsor does conclude that metronidazole clearly demonstrates a greater incidence of pulmonary tumors in mice and "other tumors" in rats.

Photocarcinogenicity Potential:

The ability of metronidazole to enhance the carcinogenic potential of UV irradiation was evaluated in albino hairless mice. The study was reported by Kelly *et al.* (1989). SKH-hrl female mice (18 or 32 animals/group) were irradiated 5 days per week for 12 weeks. The initial UVR fluence was 0.53 J/cm² and was increased by 20% every 2 weeks to allow for the protective effect of epidermal thickening. After 12 weeks and until time of death, the UVR fluence was held at a fluence of 1.6 J/cm² while the frequency of UV irradiation was reduced to twice per week. Drug therapy was begun two weeks following the first UVR exposure and was given on the same days as UV irradiation. On each occasion metronidazole in saline (pH 7) was given

intraperitoneally 2 hours prior to UVR. The drug dosage was 15 ug/g body weight.

The light source consisted of a bank of 6 fluorescent 40 watt tubes comprising one UVB (Oliphant FL40SE), three UVA (Sylvania F40/350BL), and two True-Like (Dura-Test Corporation, USA) tubes contained on a double batten. A broad spectrum light source was used because of the possibility of photoaugmentation by visible and infrared wavelength. The emission spectrum was measured between 250 and 700 nm using a computer-controlled McPherson grating-monochromator. The distance of the animals was 16 cm from the light source. The UV flux under the exposed light area was between 2.00 and 2.35 mW/cm².

Mice were inspected twice weekly for tumor development and the rate of onset of tumors and the number of tumors per mouse were recorded. At 30 weeks after the start of UVR, all mice were killed and their skin tumors collected, fixed in formalin, and sections stained with hematoxylin and eosin for microscopic classification.

In the control animals (saline-treated; 32/group), skin tumors first appeared 126 weeks following the start of UVR and were confined to the dorsum of the animals. All control mice had at least one skin tumor by the end of the study. Macroscopically, the tumors were distinguished as papillomas, papules, and endophytic tumors. Histologically, papillomas were confirmed as benign lesions although occasionally evidence of pleiomorphism suggestive of premalignancy was present. Papules were largely carcinomas in situ and, less commonly, focal epidermal hyperplasia. Endophytic tumors were either squamous cell carcinoma or keratoacanthoma.

UVR-induced carcinogenesis was enhanced by the intraperitoneal administration of metronidazole. Metronidazole-treated mice were killed at week 25 because of the debilitation associated with the high tumor burden. Using the one-way analysis of variance procedure, the incidence of tumors at week 20 and 25 was statistically significantly greater than the incidence in control animals for the same corresponding period. Table 1 listed the mean number of tumors per mouse during the study. The type of tumor observed in the metronidazole-treated group were papillomas (47%), keratoacanthoma (9.5%), carcinoma (41.5%) and other (2%). For the control animals, the frequency of tumors was 66.7%, 3.3%, and 30%, respectively. In addition, metronidazole (30 ug/g) also potentiated the effect of UVR following intraperitoneal administration for 3 consecutive days and a single dose of UVR (fluence was 528 mJ/cm²) on the second day.

Table 1. Mean incidence of skin carcinogenesis expressed as the number of tumors per mouse as a function of time following metronidazole and UV treatment.

Drug	No. of Animals	Week 15	Week 20	Week 25
Control	32	0	0.37 ± 0.11	0.83±0.29
Metronidazole	18	0.38±0.14	3.56±0.45	5.63±0.56

In summary, the intraperitoneal administration of metronidazole followed by UV irradiation potentiates the phototoxic effect and enhances UV carcinogenesis in the hairless mouse.

Mutagenicity Studies

The literature is summarized below:

The mutagenicity potential of metronidazole reported in the literature has been examined in several *in vitro* tests using mammalian cells systems. Positive results were reported with *in vitro* test systems assessing the potential of metronidazole to cause chromosome aberrations under anaerobic conditions in Chinese hamster V79-379A cells, anoxic lymphocytes, and human lymphocytes, toxicity and mutagenicity to V79 cells treated as spheroids, TA 100, WP2uvRA-, and TA 98, abnormal anaphases in Chinese hamster ovary (CHO) cells, and DNA single-strand breaks in rat hepatocytes. No significant differences in sister chromatid exchanges were observed within treatments or between metronidazole-treated and control when hamster BHK-21 and CHO-K1 cells in culture were exposed to 0.1-10 mM metronidazole or to 0.5 mM for 648 hours. Negative results were also reported in other studies examining the potential of metronidazole to cause sister chromatid exchanges in CHO cells, Chinese hamster V79 cells and human lymphocytes, gene mutations in L5178Y mouse lymphoma cells, base pair and frameshift mutations in V79 cells, chromosomal abnormalities in lymphocytes with good oxygenation, and inhibition of DNA synthesis and DNA-repair in human lymphocytes.

The mutagenic potential of metronidazole has also been investigated using *in vivo* mammalian test systems. Metronidazole did not induce sister chromatid exchanges in Chinese hamster administered up to 500 mg/kg and did not induce heritable translocation in mice given up 750 mg/kg/day for eight weeks. In the dominant lethal test, no mutagenic activity was observed in mice dosed with up to 1000 mg/kg/day for 5 weeks or in rats dosed with 600 mg/kg/day for 5 days. Negative results were also reported in the micronucleus test. Rats given up to 100 mg/kg and mice given up to 4000 mg/kg or 100 mg/day for 7 days did not exceed the micronucleus frequency of controls. In addition, no excess chromosomal aberrations in circulating human lymphocytes were observed in patients treated for 8 months and women treated for 7 days with 600 mg of oral metronidazole. However, conflicting results were obtained following intraperitoneal injections of either 23, 70, or 160 mg/kg of metronidazole to mice. A significant dose-dependent increase was observed in the frequency of micronuclei. Moreover, a significant increase in the chromosome aberration frequency was observed in lymphocytes taken from patients with Crohn's disease who had been treated with 200-1200 mg/day of metronidazole for 1 to 24 months.

Metronidazole was mutagenic to certain strains of Salmonella typhimurium and to mice after intraperitoneal injections, but did not cause chromosomal aberrations or sister chromatid exchanges in human lymphocytes. However, metronidazole was highly cytotoxic to mammalian cells and capable of giving rise to chromosomal aberrations under hypoxic conditions. ✓

Reproduction Studies

The literature is summarized below:

The teratogenic potential of metronidazole was evaluated in rats, guinea pigs, rabbits, and mice. In rabbits, the compound was administered orally at dose levels of 30-200 mg/kg/day

during day 3 to day 13 of gestation. Neither embryotoxic nor teratogenic effects were reported in any of these four studies performed. In five of the six rat studies, metronidazole was administered either at a dietary concentration of 0.13% for 18 days of gestation, or by gastric intubation at dose levels from 50-200 mg/kg/day for periods ranging from 10 days (midgestation) to 40 days (before and during pregnancy). No teratogenic or embryotoxic effects were observed in any of these five studies.

However, a sixth study reported embryotoxic and teratogenic effects. In this latter study, rats received dietary doses of 10 mg/kg/day for an unspecified period during pregnancy. In addition, this latter study reported that metronidazole was embryotoxic and teratogenic effects in guinea pigs and mice receiving gastric intubations of 7-9 mg/kg/day for 7-10 days of gestation and dietary doses of 10-11 mg/kg/day for 10 days, respectively. The incidence of premature births, birth defects, and still births were increased in all three species.

Mildly fetotoxic and teratogenic findings were reported in a second mouse study in which Swiss Webster mice received intraperitoneal injections of 15 mg/kg/day of metronidazole and ethyl alcohol on day 8, 10, 12, and 14 of pregnancy. The effects recorded were increases in fetal deaths per litter and increases in fetal malformations. A third mouse (Swiss) study found no evidence of teratogenicity after animals were given oral administrations of 10 and 20 mg/kg/day during Day 6 to Day 15 of gestation.

The adequacy of several of the above studies is discussed in the Comment section of this review.

Special Toxicity Studies

The primary dermal irritation studies, performed at _____ are summarized below:

The potential for 0.75% metronidazole in a gel, cream, and lotion, and the vehicle for each formulation to elicit an irritant response was assessed in intact and abraded New Zealand White rabbit skin (Study No. 002:3200:0694, 003:3200:0694, 004:3200:0694, 005:3200:0694, 008:3200:0894, 009:3200:0894, 015:3200:0894, and 016:3200:0894). Six NZW rabbits, about 3 months of age and weighing 2 kg, and sex unspecified, were obtained from a licensed dealer. Twenty-four hours prior to test initiation, the animals were prepared for testing by close-clipping the hair of the mid-dorsal area of the trunk, between the scapulae and the pelvis. Two test sites, each 2.5 cm² on each side of the vertebral column, were chosen. The left side was intact while the right side was abraded with a sterile 22 gauge hypodermic needle. A single application of 0.5 ml of material was applied on each site for 24 hours. The test sites were occluded with wrapping. After 24 hours, the wrapping was removed and the remaining test article was washed from the skin. Each test site was individually examined and scored at 24 and 72 hours, for erythema and edema, using the Draize skin scoring scale. Following the 72 hour reading, the mean scores for 24 and 72 hour gradings were averaged to determine the primary skin irritation index. A score of 5 or more indicates a primary dermal irritant.

Results - The primary irritation index scores for the vehicles of each formulation (gel, cream, and

lotion) were 0.43 (0.10), 1.68, and 1.03, respectively. Since the gel was examined twice, two scores are reported. The primary irritation index scores for metronidazole in the gel, cream, and lotion were 0.50 (.35), 1.68, and 1.25, respectively. The results are considered to be only mildly irritating. Thus, the metronidazole-containing formulations or their respective vehicle are not considered to be a primary dermal irritants.

Absorption, Distribution, Metabolism, and Excretion Studies

1. The *in vitro* penetration of 0.75% (w/w) metronidazole contained in two different formulations (cream and gel) was compared across human non-occluded full thickness skin maintained in dynamic (flow-through) diffusion cells with an hourly flow rate/cell volume ratio equal to 1 during 12 hours.

The study was conducted at Galderma CIRD during February/March, 1994. The formulations of metronidazole were MetroGel® 0.75% (batch GDCA) from Curatek and Metronidazole cream 0.75% (batch 3D0547) from Cynamid Canada. Human female mammary (3) and abdominal (1) skin removed during operations were used in all experiments. The source was the A. Pare Hospital, Marseille, France. Four different donors were used with 12 cells per formulation. A target dose of 10 mg of formulation (75 ug of metronidazole) was applied to a surface of 1 cm² by cell. The application schedule was performed according to a randomization design including effects of skin origin, cell or skin thickness, and formulation. Metronidazole was measured in receptor fluid fractions, epidermis, dermis, non-absorbed surface excess, and cell washings.

Results - The total cutaneous penetration estimated after 12 hours (skin plus receptor fluid content) was around 51% for the gel while it was 42% for the cream formulation. Although a lower content of metronidazole (8% versus 14%) was observed in the receptor fluid of the cream formulation, a similar level of metronidazole was reported in the epidermis and dermis for both formulations (33% with the gel and 25% with the cream). The mass balance for each formulation were also similar; 97% recovery found in the gel while an 82% recovery was observed in the cream. The incomplete balance may be due to losses in recovery of the parent compound or skin transformation to other products.

2. The *in vitro* penetration of 0.75% (w/w) metronidazole contained in two different formulations (lotion and gel) was compared across human non-occluded full thickness skin maintained in dynamic (flow-through) diffusion cells with an hourly flow rate/cell volume ratio equal to 1 during 15 hours.

The study was conducted at Galderma CIRD during June/July, 1994. The formulations of metronidazole were Rozex Gel® 0.75% (batch 1C19010) from Lederle and Metronidazole lotion 0.75% (batch 562.203/2F1) from Galderma CIRD. Components of the formulations were

not identified. Human female mammary (4) skin removed during operations were used in all experiments. The source was the A. Pare Hospital, Marseille, France. Four different donors were used with 12 cells per formulation. A target dose of 10 mg of formulation (75 ug of metronidazole) was applied to a surface of 1 cm² by cell. The application schedule was performed according to a randomization design including effects of skin origin, cell or skin thickness, and formulation. Metronidazole was measured in receptor fluid fractions, epidermis, dermis, non-absorbed surface excess, and cell washings.

Results - The total cutaneous penetration estimated after 15 hours (skin plus receptor fluid content) was around 32% for the gel while it was 9% for the lotion formulation. Although a lower content of metronidazole was observed in the penetration estimate, the mass balance for each formulation were similar; 83% recovery reported for the gel while an 74% recovery was observed in the lotion. The incomplete balance may be due to losses in recovery of the parent compound or skin transformation to other products.

3. Subchronic (4 weeks) toxicity study by the cutaneous route in Sprague Dawley strain of rat of Rozex lotion and Rozex gel containing metronidazole at 0.75%. Pharmacokon Europe, Report Number 1.CG.03.SRE.8163.GDL (submitted in IND and NDA 19-737)

This study was conducted in accordance with GLP practices from September to October 1994 at CIRD Galderma, France. The toxicity of Rozex[®] lotion (containing 0.75% metronidazole) and Rozex[®] gel Lederle (containing 0.75% metronidazole) was evaluated in Sprague-Dawley rats (5/gender) following 28 daily dermal applications. Rozex Lotion (Batch No. 562.203/2F2) was manufactured and packaged by Galderma Laboratories, France, while the Rozex Gel (no batch number given) was commercially manufactured by Lederle Laboratories. Excipients are not identified. Satellite groups of animals (5/sex in treated and 2/sex in control) were also treated to evaluate toxicokinetics parameters for metronidazole. Each dose was given as a 2 ml/kg administration and the duration of exposure was 6 hours a day. Control animals were included but remained untreated. The applied formulations were equivalent to doses of 15 mg/kg or 0.01 mg/cm². Animals wore collars to help prevent ingestion of test material.

Animals were observed for clinical changes daily and local cutaneous irritation was scored each day just before the application. Body weights and food consumption were recorded once a week while blood samples were collected (via orbital plexus) at necropsy. At necropsy, a gross post-mortem examination was conducted and selected organs were processed for histopathologic examination, including the femur. Toxicokinetic monitoring of systemic exposure was performed at 2, 4, 8, and 24 hours post-dosing on Day 1 and Day 28.

Mean serum levels at 4 hours post-dosing of Rozex lotion increased from 207 ng/ml (68-635 ng/ml) on day 1 to 736 ng/ml (114-1651 ng/ml) on day 28 in male animals. In females, the increase went from 170 ng/ml (105-233 ng/ml) at day 1 to 922 ng/ml (108-3461 ng/ml) at day 28. For the gel, male animals had a 4-hour post-dosing mean serum level of 75 ng/ml (28-102 ng/ml) at day 1 and 559 ng/ml (98-1701 ng/ml) at day 28. In females, the 4 hour-post-dosing mean serum level of metronidazole was 84 ng/ml (45-118 ng/ml) at day 1 and

705 ng/ml (132-1520 ng/ml) at day 28.

Formulation	Males Day 1	Males Day 28	Females Day 1	Females Day 28
Gel	75	559	84	705
Lotion	207	736	170	922

*-Values were obtained from blood samples collected 4 hours after administration.

In summary, topical administration of metronidazole does cause a 4 to 8 fold increase in serum levels following 28 days of applications. The increase in serum levels appears to be greater in females for each formulation compared to male animals. However, statistical analysis was not conducted. Additionally, metronidazole serum levels appear to be greater in animals treated with the lotion compared to gel formulation for that time period.

A summary of the literature is provided.

Metronidazole is completely and promptly absorbed after oral administrations. At least 80% of the drug is absorbed within 1 hour after dosing rats and the mean peak concentration of labeled material in blood is 9.6 ug/ml at 1 hour after an oral administration of 10 mg/kg. The half-life of clearance of radioactivity from the majority of tissues is between 3 and 4 hours. In the blood, the half-life clearance of unchanged metronidazole is 3.2 hours in rats. About 20% of the compound is bound to plasma proteins. Metronidazole penetrates well into body tissues and fluids including vaginal secretions, seminal fluids, saliva, and breast milk after oral and intravenous administrations. The native drug and its metabolites have been transferred to suckling human infants by the breast milk. The highest concentration is found in the liver and the lowest is observed in the fat. A similar pattern in distribution is observed after oral and intravenous administrations in mice, rabbits, and rats. This compound can readily pass the human blood-brain and placental barriers. The liver is the main site of metabolism and the principal metabolites result from oxidation of side chains and formation of glucuronides. The metabolism is similar with species-related differences including humans in qualitative and quantitative amounts of oxidized and conjugated metabolites. Both unchanged metronidazole and several metabolites are excreted in various proportions in the urine of animals and man after administration. The principal metabolites, 1-(2-hydroxyethyl)-2-hydroxy methyl-5-nitroimidazole and 1-acetic acid-2-methyl-5-nitroimidazole, have anti-trichomonal activity. Urinary excretion accounts for 50-65% of the dose excreted as metronidazole within 24 hours after administration while fecal excretion accounts for 12-16% at 24 hours. A similar pattern is observed after administration to humans.

In humans, a single oral 500 mg dose will result in plasma concentrations of about 10 ug/ml after approximately one hour. The repeated administration of this same dose every 8 hours lead to a C_{max} of 19.8 ug/ml at steady state. Following intravenous administration of the same

dose and regimen, steady state C_{max} value is slightly higher. In comparison, the topical administration of 1 g of a 0.75% metronidazole gel (75 mg) to ten rosacea patients showed a maximum serum concentration ranging from undetectable to ng/ml. For most samples, serum concentrations were below the detection limit of the assay (ng/ml) and an accurate estimation of the AUC was not possible. In adults with rosacea who received a daily application to the face of metronidazole doses averaging 3.75 mg as a 1% topical cream for one month, the serum concentrations of the drug ranged from undetectable to ng/ml. The *in vitro* comparison between the gel and topical cream suggest that the percutaneous absorption of metronidazole in the cream is not expected to be higher than with the gel. The reported mean half-life of the drug ranges from 6 to 10 hours irrespective of the route of administration (iv and oral). The total body clearance of metronidazole is 70 to 90 ml/min after a single oral administration of 500 mg.

Comments:

Metronidazole (0.75%) in a gel has been approved and marketed for the treatment of rosacea in the United States since 1988. Although clinical efficacy has been reported for the treatment of rosacea, the mechanism by which metronidazole ameliorated the lesions and erythema of rosaceae is not known. Prior to the approval for this indication, metronidazole was approved in the United States in 1963 as an oral drug for the treatment of trichomonal infections.

The topical administration of metronidazole has only resulted in an increase incidence of leukopenia in female rats following 4 weeks of administration with either the lotion or gel formulation of 0.75% metronidazole. This finding has not been reported in other non-clinical studies and many of the findings from this study were difficult to interpret without the use of additional treatment groups or larger group sizes. However, the 60% decrease in white blood cell count was observed in both treatment groups and leukopenia has been observed in humans orally treated with metronidazole (600-800 mg for 7-10 days) for trichomoniasis (Roe, *Surgery* 1983;92:158-164). This 4-week toxicity study is the longest dermal toxicity study performed with metronidazole. Whether the leukopenia observed in the 4-week dermal toxicity study is associated with the route of administration, a more adequate dermal study would better establish the association of the leukopenia and route of administration with treatment to metronidazole.

The long-term (18 to 92 weeks) oral administration of metronidazole (300 and 600 mg/kg/day) decreased the rate of weight gain and altered the male reproductive system in rats and mice, respectively. Doses of 150 mg/kg/day for 78 or 92 weeks in either species did not alter the male reproductive system. Metronidazole can cause morphological changes in the spermatozoa of mice. In rats, reduced spermatogenesis and marked testicular degeneration were also observed following dietary doses of 400 mg/kg/day for 8 weeks. The no-observable-effect doses in mice and rats are approximately 70 times and 140 times greater than the maximum possible human systemic exposure after a topical administration. This estimate was obtained assuming 100% bioavailability of the oral dose to the animals (a 150 g rat with a surface area of 250 cm² and a 20 g mouse with 70 cm² surface area; conversion factor of 6 and 3 to get mg/m², respectively) and 47% absorption of the topical human dose (3 g of cream) on a 60 kg individual (surface area = 16200 cm²). Currently, the Sponsor does not include any of these findings in the proposed label. These findings need to be described in the proposed label.

Oral doses (either feeding or gavage) of metronidazole also resulted in higher incidences of tumors in mice and rats, but not in hamsters compared to control animals. Mice primarily developed pulmonary tumors following dietary (187 mg/kg/day) or gavage (66 mg/kg/day) dosing. In rats, the more prominent lesions were mammary tumors following dietary (270 mg/kg/day) or gavage (30 mg/kg/day) dosing. These findings were observed in different strains of rodents, duration of treatments, doses, and method of administration. The no-observable-effect dietary doses used in the rat and mouse studies (135 mg/kg/day and 150 mg/kg/day) approximate 120 and 70 times, respectively, the maximum possible human systemic exposure after a topical administration of 3 grams of lotion. The proposed label does not provide an adequate description of the findings observed in these studies. These findings need to be described in further detail in the label.

Metronidazole was mutagenic to certain strains of *Salmonella typhimurium* (TA 100 and TA 98) and *E. coli* strain WP2uvRA-. Furthermore, a dose-dependent increase in the frequency of micronuclei was observed in mice after intraperitoneal injections of either 23, 70, and 160 mg/kg of metronidazole. In humans with Crohn's disease who were treated with 200-1200 mg/day of metronidazole for 1 to 24 months, a significant increase in the chromosome aberration frequency was reported. However, other genotoxic studies gave negative results. Embryotoxicity and teratogenicity were reported in two rat, one guinea pig, and two mouse studies. Several of the reproductive studies have been previously reviewed by FDA Pharmacologists Harold Carlin and Sandra Morseth (see attached reviews) and were invalidated due to lack of controls (Ivanov, 1969), unreliable results (rabbit studies performed by investigator incompetence (rat studies performed by _____ and possible mechanical damage during intraperitoneal dosing (Giknis & Damianov, 1983). The remaining studies report negative reproductive findings. The highest doses examined in these studies (200 mg/kg/day in rats and 20 mg/kg/day in mice) represent 180 and 9 times, respectively, the maximum possible human systemic exposure after a topical administration. Because metronidazole is a carcinogen, and is capable of crossing the placental barrier and entering the fetal circulation rapidly, the drug should be used during pregnancy only if clearly needed. The marketed formulations of metronidazole are designated Pregnancy Category B products. For this product, the same pregnancy category is recommended.

The absorption of metronidazole after a topical administration will result in low systemic plasma concentrations when compared to an oral or intravenous administrations. This low systemic exposure will minimize the potential for a toxic systemic insult. Although a low systemic exposure of metronidazole will occur with a topical application, the ultraviolet absorption of metronidazole indicates that this compound may become activated or decompose to yield a reactive intermediate. Under the conditions used by Kelly *et al.* (1989), metronidazole did elicit a phototoxic response in albino hairless mice. More importantly, the intraperitoneal administration of 15 mg/kg/day metronidazole followed 2 hours by UVR of the dorsum caused an enhanced incidence of tumors compared to irradiated albino hairless mice.

Because of morphological differences between mouse skin and human skin, the mouse may be more sensitive than humans to the phototoxic potential of metronidazole. The phototoxic potential of metronidazole gel or cream was evaluated in several clinical Phase I trials. Both formulations were examined for the ability of metronidazole to elicit a photoirritation or

photoallergic reaction in normal human volunteers. Under the conditions of these studies, no evidence for either metronidazole (0.75%) or its vehicles (gel or cream) to elicit such a response was observed during the treatment period (single exposure or 6 exposures over a 3 week period).

The relevance of the enhanced photocarcinogenesis observed in mice due to metronidazole to humans is not known. The administration of metronidazole was approximately 8 times the human systemic exposure. Also, each drug administration was by the intraperitoneal route while the irradiation was on the dorsum. Thus, the actual levels of metronidazole at the site of irradiation was much lower following absorption and distribution of the intraperitoneal treatment. However, cutaneous differences in structure or physiology among mice and humans make the findings from this study difficult to extrapolate. In all, this study does indicate that the potential for increased skin cancer development with the prolonged used of metronidazole in combinatin with causal sun exposure.

Overall, metronidazole does not elicit sensitization reactions following topical application. However, the compound does impair the male reproductive system and is a carcinogen in rodents. Also, metronidazole in combination with solar irradiation does enhance the incidence of tumors following prolonged exposure.

Recommendations:

1. The Sponsor is recommended to incorporate into the label the effect observed on male rodent fertility following oral administration of metronidazole in accordance with CFR 201.57.
2. The Sponsor is recommended to expand the content of the Carcinogenesis, mutagenesis, impairment of fertility subsection of the label in order to describe the doses used in the carcinogenicity including the photocarcinogenicity studies, type of tumors observed, and how the doses used in the animal studies compare to human exposure. When calculating the human equivalent, the Sponsor is recommended to use systemic exposure or extrapolate on the basis of body surface area.

/S/

3/24/98

Javier Avalos, Ph.D.
Toxicologist

cc:
NDA 20-901
HFD-540
HFD-540/Pharm/Avalos
HFD-540/Pharm/Jacobs
HFD-540/CSO/Kummerer
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For Concurrence Only:
HFD-540/DD/JWilkin 3/27/98
HFD-540/Team Leader/Jacobs 3/24/98

HFD-540/Chem/Higgins

APPEARS THIS WAY
ON ORIGINAL

**Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products (HFD-540)**

JUL 22 1998

NDA 20-901 (BL)

Date Submitted: July 10, 1998

Number of Volumes: 1

Date CDER Received: July 13, 1998

Date Assigned: July 16, 1998

Drug: Metronidazole 0.75% lotion (MetroLotion™)

Chemical Name: 2-methyl-5-nitro-1H-imidazole-1-ethanol

Category: Antibacterial and antiprotozoal agent

**Sponsor: Galderma Laboratories, Inc.
3000 Alta Mesa Blvd., Suite 300
Forth Worth, Texas 76133
(817) 263-2676**

Indication: For the treatment of rosacea

Route of Administration: Topical

Submissions Cross-referenced:

DMF	DMF	DMF	DMF
IND	NDA 19-737 (Metrogel [®])		
IND	NDA 20-531 (MetroCream™)		
IND	(MetroLotion™)		

Background: Metronidazole in a cream (NDA 20-531) and gel (NDA 19-737) formulation is approved for the treatment of rosacea. Galderma received approval for marketing of MetroGel on November 22, 1988 and MetroCream on September 20, 1995. In the review of the NDA for the lotion formulation, several recommendations were made pertaining to the label of the product. In the current submission, the Sponsor has submitted a revised draft labeling amendment. However, none of the recommendations made regarding the label were incorporated. The recommendations made were as follows:

- 1. The Sponsor is recommended to incorporate into the label the effect observed on male rodent fertility following oral administration of metronidazole in accordance with CFR 201.57.**
- 2. The Sponsor is recommended to expand the content of the carcinogenesis, mutagenesis, impairment of fertility subsection of the label in order to describe the doses used in the carcinogenicity including the photocarcinogenicity studies, type of tumors observed, and**

how the doses used in the animal studies compare to human exposure. When calculating the human equivalent, the Sponsor is recommended to use systemic exposure or extrapolate on the basis of body surface area.

Comments:

The Code of Federal Regulations requires that specific information regarding the content and format of the label be incorporated into the label of prescription drug products. The current revised draft label submitted by the Sponsor does not meet this requirement. Again, the Sponsor will be advised to include the non-clinical data pertinent to the label in accordance with CFR 201.57.

Conclusion: The Sponsor needs to incorporate and expand several sections of the label for the MetroLotion Topical Lotion drug product in accordance with CFR 201.57.

Recommendations:

1. The Sponsor is recommended to incorporate into the label the effect observed on male rodent fertility following oral administration of metronidazole in accordance with CFR 201.57.
2. The Sponsor is recommended to expand the content of the Carcinogenesis, mutagenesis, impairment of fertility subsection of the label in order to describe the doses used in the carcinogenicity including the photocarcinogenicity studies, type of tumors observed, and how the doses used in the animal studies compare to human exposure. When calculating the human equivalent, the Sponsor is recommended to use systemic exposure or extrapolate on the basis of body surface area.

/S/

7/22/98

Javier Avalos, Ph.D.
Toxicologist

cc:
NDA 20-901
HFD-540
HFD-540/Pharm/Avalos
HFD-540/Pharm/Jacobs
HFD-540/CSO/Wright
HFD-540/MO/Huene
HFD-540/Chem/Timmer

For Concurrence Only:
HFD-540/DD/JWilkin *9w 8/4/98*
HFD-540/Team Leader/Jacobs *7/22/98*

**Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products (HFD-540)**

OCT 16 1998

NDA 20-901 (BL)

Date Submitted: October 2, 1998
Number of Volumes: 1
Date CDER Received: October 5, 1998
Date Assigned: October 8, 1998

Drug: Metronidazole 0.75% lotion (MetroLotion™)
Chemical Name: 2-methyl-5-nitro-1H-imidazole-1-ethanol
Category: Antibacterial and antiprotozoal agent

Sponsor: Galderma Laboratories, Inc.
3000 Alta Mesa Blvd., Suite 300
Forth Worth, Texas 76133
(817) 263-2676

Indication: For the treatment of rosacea

Route of Administration: Topical

Submissions Cross-referenced:

DMF	DMF	DMF	DMF
IND	NDA 19-737 (MetroGel [®])		
IND	NDA 20-531 (MetroCream™)		
IND	(MetroLotion™)		

Background: Metronidazole in a cream (NDA 20-531) and gel (NDA 19-737) formulation is approved for the treatment of rosacea. Galderma received approval for marketing of MetroGel on November 22, 1988 and MetroCream on September 20, 1995. In the review of the NDA for the lotion formulation, several recommendations were made pertaining to the label of the product. The recommendations made were as follows:

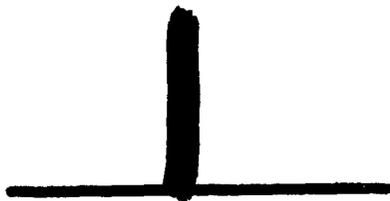
1. The Sponsor is recommended to incorporate into the label the effect observed on male rodent fertility following oral administration of metronidazole in accordance with CFR 201.57.
2. The Sponsor is recommended to expand the content of the carcinogenesis, mutagenesis, impairment of fertility subsection of the label in order to describe the doses used in the carcinogenicity including the photocarcinogenicity studies, type of tumors observed, and how the doses used in the animal studies compare to human exposure. When calculating the human equivalent, the Sponsor is recommended to use systemic exposure or extrapolate on the basis of body surface area.

In addition, the Sponsor was encouraged to incorporate the effects observed on hematological parameters following the use of metronidazole. In the current submission, the Sponsor has submitted a revised draft labeling for review. However, the current draft label does not adequately address all the recommendations made in the previous memos sent to the Sponsor.

Comments on Proposed Draft Label:

In general, the Sponsor has incorporated the recommendations made in earlier memos to the Sponsor. These included incorporating the findings from the non-clinical carcinogenicity, mutagenicity, and photo co-carcinogenicity studies. In addition, the Sponsor was encouraged to incorporate the effects observed on rat and mice spermatogenesis and the effect observed on hematological parameters following the use of metronidazole. However, the Sponsor did not emphasize in the label for patients to avoid solar exposure as much as possible. The reason for a greater precaution from solar exposure is that the incidence of tumors in mice increased following the intraperitoneal administration of metronidazole in combination with solar radiation. Also, the Sponsor has fully described the rat carcinogenicity effects observed following treatment with metronidazole. In this case, the Sponsor has only used the findings from one rat carcinogenicity study to calculate the human equivalent exposure when a second rat carcinogenicity study also found similar findings but at a lower dose of metronidazole. Thirdly, the data available for metronidazole regarding the inhibition of rat spermatogenesis suggest that a lower effect dose (300 mg/kg/day) exists than the one used by the Sponsor (400 mg/kg/day) to calculate the human equivalent. Thus, the sponsor is encouraged to revise their current draft label to incorporate the following recommendations:

Redacted



pages of trade

secret and/or

confidential

commercial

information

Conclusion: The Sponsor has addressed the majority of the recommendations made regarding the generation of an adequate label as stated in CFR 201.57. However, several changes are recommended for the current revised draft label submitted by the Sponsor.

Recommendations:

1. In the **Precaution** section, the Sponsor is encouraged to incorporate a statement which encourages patients to avoid or minimize sun exposure. For example:

This statement

could be included in the **General** subsection or the **Information for patients** subsection of the **Precaution** section.
2. In the **Carcinogenesis** section, the following changes are recommended:

/S/

10/15/98

Javier Avalos, Ph.D.
Toxicologist

cc:

NDA 20-901

HFD-540

HFD-540/Pharm/Avalos

HFD-540/Pharm/Jacobs

HFD-540/CSO/Wright

HFD-540/MO/Huene

HFD-540/Chem/Timmer

For Concurrence Only:

HFD-540/DD/JWilkin

HFD-540/Team Leader/Jacobs e J 10/16/94

APPEARS THIS WAY
ON ORIGINAL