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APPLICATION NUMBER: NDA 20-743

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

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20743

Submission Dates: 10/2/96, 2/4/97

Generic Name, Strength and Formulation: Metronidazole 1% Cream

Brand Name: Noritate®

Date Assigned: 10/21/96

MAY 5 1997

Applicant: Dermik Laboratories, Inc.

Final Review Date: 5/2/97

Submission Code: 3S

Reviewer: Kofi A. Kumi, Ph.D.

SYNOPSIS:

The applicant is seeking approval for the use of metronidazole 1% cream to treat acne rosacea. The applicant studied the systemic availability after a single application of 1 gm metronidazole 1% cream to the face of sixteen healthy volunteers. Metronidazole concentrations were detected in 7 out of 16 subjects who participated in the study. The maximum concentration (C_{max}) in these subjects was detected 8- 12 hours post application. The mean \pm SD (range) was 27.6 ± 7.3 (22.3 - 43.5) ng/mL. In a supportive study, percutaneous absorption and systemic availability was evaluated in sixteen healthy volunteers after application of radiolabeled 2% metronidazole cream (approximately 100 mg) was applied to a 9 cm² area between the shoulder blades for 12 hours. Eight patients had their skin stripped. The mean \pm SD total recovery in intact and stripped skin were 96.6 ± 2.8 % and 97.6 ± 2.4 % of administered dose, respectively. Of the amount observed from the intact skin and stripped skin, 94.3 ± 3.3 % and 93.2 ± 6.9 %, respectively were found in the Q-tips used to remove the dose after the application period. This suggested that systemic availability after single dose topical application of 100 mg of 2% metronidazole was very low.

The applicant submitted a literature article in which 81 patients with rosacea were treated either with 1% metronidazole cream or placebo. Serum concentrations were determined in 40 patients who were treated with metronidazole cream. The average amount of metronidazole applied to the face was 3.75 mg/day. Traces of serum metronidazole, ranging from _____ ng/mL, were reported detected in 10 of 40 patients. Oral metronidazole has been used to treat acne rosacea. The minimum oral metronidazole dose needed to see improvement of rosacea on a patient is reported to be 200 mg/day. A single dose of 250 mg oral metronidazole is reported to produce a maximum metronidazole concentration in 1 hour of 4-7 μ g/mL.

The concentration of metronidazole cream detected in plasma after topical application was less than 1% of that reported after oral administration. 1% metronidazole cream has very low systemic availability after topical application to the face.

REVIEW:

Background:

This review contains a summary of the studies submitted to section 6 (Human Pharmacokinetic and Bioavailability) in support of NDA 20743. Metronidazole is currently available in oral, injectable and topical dosage forms. The current topical dosage formulations available include metronidazole 0.75% cream by Galderma Laboratories Inc. and has been approved for treatment of rosacea. The current NDA is for 1% metronidazole cream and seeking approval for the topical treatment of rosacea including inflammatory papules, pustules and erythema. The studies submitted under the pharmacokinetic section of the NDA evaluated the percutaneous absorption of metronidazole after topical application of the 1% cream. The applicant submitted one pivotal study (DL-6027-9620), two supportive studies (ICP 63/0003 and ICP 63/0001) and two literature articles in the pharmacokinetic section of the NDA. It was recommended by Dr. Bashaw at the NDA filing meeting that since plasma concentrations were not detectable, the applicant perform in vitro skin penetration study using human cadaver skin and Franz cells. Instead of performing this test, the sponsor refined the assay procedure to improve the sensitivity of the assay used in the analyses of the samples obtained from the pivotal study.

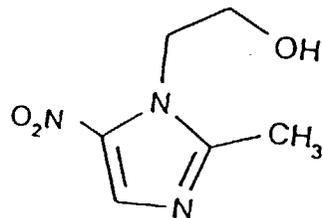
Metronidazole is a nitroimidazole derivative, which is about 10-20% bound to serum proteins and has a plasma half-life of 6-12 hours. It is metabolized in the liver; the major metabolites are hydroxymetronidazole and acetic acid metronidazole. Hydroxymetronidazole possess about 30% of the biological activity of the parent compound. Approximately 70-80% of a given dose is excreted renally with about 20% excreted unchanged.

Metronidazole is classified therapeutically as anti-bacterial and anti-protozoa agent. The mechanism of action of metronidazole in treating rosacea is not known; however, it is postulated to be related to its inhibitory effect on inflammatory neutrophil cell function. Antibacterial and anti-protozoa agents such as oral metronidazole and tetracycline have been used effectively in the treatment of rosacea. However, therapy with systemic tetracycline and metronidazole are associated with adverse effects that include gastrointestinal irritation, hepatic and renal toxicity, phototoxicity, vaginal candidiasis, neurologic and hematologic disturbances. The advantage of topical formulation in treating rosacea is reported to be that they are not associated with the severe adverse effects due to low systemic concentrations after topical administration. Metronidazole 1% topical cream will be applied once daily in contrast to the twice daily application for the current marketed 0.75% cream.

Physicochemical Properties:

Metronidazole:

Structure of metronidazole is provided below.



Chemical Name: 2-methyl-5-nitroimidazole-1-ethanol.

Molecular Formula: C₆H₉N₃O₃

Molecular Weight: 171.16

Pka: 2.5

Solubility: Sparingly soluble in water, slightly soluble in ethanol (95%) and very slightly soluble in ether and chloroform.

Formulation:

Ingredient	Quantity/Gram
✓ Metronidazole, USP, micronized	10 mg
✓ Stearic Acid, NF	mg
✓ Glyceryl Monostearate, NF (Myverol 18-07)	mg
✓ Glycerin, USP	mg
✓ Methylparaben, NF	mg
✓ Propylparaben, NF	mg
✓ Triethanolamine, NF	mg
✓ Purified Water, USP	mg

Indication (Per draft Label):

ANALYTICAL METHODS:

OVERVIEW OF BIOAVAILABILITY AND PHARMACOKINETIC STUDIES:

DL-6027-9620: Single Dose Pharmacokinetics of Topical Metronidazole 1% Cream in Normal Adults (Volume 1.10 page 10-34)

Introduction:

Percutaneous absorption studies using 1% cream conducted by Rhone-Poulenc, the parent company of Dermik Labs, in 1985 indicated very limited absorption. The formulation used in those studies is reported to be different from the current proposed metronidazole 1% cream that Dermik wants to market for the treatment of rosacea. This study is to evaluate the systemic availability of Dermik's 1% metronidazole formulation after application to the face of healthy volunteers.

Objectives:

The objectives of this single-dose study were to assess the topical and systemic tolerance and the pharmacokinetic of 1g application of topical metronidazole 1% cream after a single application of the product.

Design:

Sixteen (8 males and 8 females) healthy volunteers participated and completed this open label, single dose study. The mean (range) age and weight (range) were 28.4 (19-59) years and 71 (51.7 -93) kg, respectively. One gram of metronidazole 1% (Lot CE 54D, manufactured by _____) was applied to the face (approximately 225 cm²) at the site on the morning of day 1 of the study. Blood samples were collected prior to dosing and at 1,2,3,4,5,6,8,12 and 24 hours after application of the dose.

Analytical Method:

Results:

No pharmacokinetic analyses were conducted because the concentrations reported were all below the limit of detection of the assay, using the original method. When the assay sensitivity was improved, the samples were reanalyzed and metronidazole concentration was detected in 7 out of the 16 volunteers (Table 1).

Table 1: Study DL 6027-9620
Subjects with Detectable Metronidazole Concentrations at any Timepoint¹
Metronidazole Concentration (ng/mL)*

Sub- ject	Sex	Pre- dose	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	8 hr	12 hr	24 hr
	m										
	f										
	f										
	m										
	m										
	m										
	f										

¹Metronidazole was not detectable at all other time points in these subjects.
ng/mL

Metronidazole concentration in 7 out 16 volunteers using refined method

In six of the patients, metronidazole concentrations were detected 8-12 hours post application of the dose. In one patient the concentration was detected at 3 hours after application of the dose. The peak concentration was observed 8-12 hours after

Radioactivity in plasma was not detected in the volunteers except in one volunteer belonging to the stripped skin group. The applicant indicated that the stripping procedure produced an abrasion in subject 4 which was slow to heal and might have contributed to the higher metronidazole levels detected. Two subjects (one from each group) had part of the dose dislodged hence were not included in the calculations. The mean \pm SD (excluding subject 4) urinary recovery in the stripped and intact skin are provided in table 2.

Table 2: Mean \pm SD (%Dose) Recovery of Radioactivity

Sample	Intact Skin (n = 7)	Stripped Skin (n = 6)
Urine	1.32 \pm 0.71	1.37 \pm 0.9
Feces	0.09 \pm 0.13	0.18 \pm 0.2
Q-Tips	94.25 \pm 3.74	93.17 \pm 6.9
Skin- Strips	0.98 \pm 0.81	0.40 \pm 0.3
Total	96.64 \pm 2.81	97.61 \pm 2.4

The mean \pm SD total recovery in intact and stripped skin were 96.6 \pm 2.8 % and 97.6 \pm 2.4% of administered dose, respectively. Of this 94.3 \pm 3.3% and 93.2 \pm 6.9% was found in the Q-tips used to remove the dose after the application period. The mean \pm SD overall (intact + stripped skin) total recovery was 97.1 \pm 2.5% of administered dose. This is indicative that very limited percutaneous penetration and absorption occurred after single dose topical application of 100 mg of 2% metronidazole when applied to both intact and stripped skin and suggests that it is not available systemically. This is consistent with what was observed in the pivotal study (9620); however, it must be noted that the skin type between the shoulder blade is different (thicker) than that on the face. The influence of different skin types on percutaneous absorption of metronidazole is not clear from the studies submitted in this application

ICP 63/0001: A Forty-Four Day Cumulative Irritation Evaluation of 3 Topical Metronidazole Patch Formulations vs Placebo Patches: Pharmacokinetic Addendum (Volume 1.11 page 162)

Introduction:

Topical metronidazole(1%) cream has been reported to be effective in treating rosacea (Nielson P.G., Br. J of Dermatology, 1983, 108:327-332). No allergic or irritant reactions were reported. This study was to further evaluate the irritation of metronidazole after 44 day application. On the last day of this study (day 44), blood samples were collected after removal of the patches to assay for metronidazole concentrations. This is primary a summary about metronidazole concentrations on day 44.

Objective:

This study evaluated the acute and cumulative irritation potential of metronidazole when applied to intact and stripped skin over a period of 44 days. An assessment for photosensitivity and for the development of allergic reactions at the site of application was conducted. To determine metronidazole plasma concentrations after 44 day of topical application.

Design:

The study was a randomized, third party blinded, intraindividual comparison in 24 healthy caucasian (male and females) volunteers who were at least 18 years of age. Three formulations of metronidazole (0.5%, 1%, 2%) and placebo patches were simultaneously applied on an uninvolved scapular region of the back of each volunteer. The 2% metronidazole and the placebo were also applied to stripped skin. The patches were secured with hypoallergenic adhesive dressing. Test materials were applied daily for 43 days and kept in place after each application for 24 hours (72 hours on weekends). Evaluations were conducted 15 minutes after removal of the patches prior to application of fresh material that day. The study was conducted on an outpatient basis with the volunteers returning to the study site each day (Monday to Friday) for evaluation and application of fresh material. Blood samples (10 mL) were collected after removal of the patches on day 44. Plasma samples were stored at -20°C prior to analysis. The limit of quantitation of the assay was 20 ng/mL.

Results:

Metronidazole was not detectable in 6 subjects; these were all female volunteers. The highest concentration detected was 58 ng/mL (Table 3, next page). There was no significant difference in plasma concentrations between male and female volunteers. In process assay validation report was not included in this report. However, the plasma concentrations detected were similar to that seen in other studies. The applicant reported that there was no evidence of acute or cumulative irritation or an allergic reaction or sensitization to any of the formulations. The applicant also reported no evidence of severe photosensitivity was observed. The results from this study were consistent with that seen in the pivotal study (9620)- there is very little systemic absorption after topical application of metronidazole cream.

Summary of Studies from the Literature Submitted in Support of Pivotal Pharmacokinetic Study:

The applicant submitted a couple of literature articles as supportive evidence for the efficacy of metronidazole in treating Acne Rosacea. These articles dealt primary with the efficacy of rosacea, however, serum concentrations of metronidazole were measured in some patients.

Aronson, I. K et al : Evaluation of Topical Metronidazole Gel in Acne Rosacea (Drug Intelligence and Clinical Pharmacy 1987 (21): 346- 351

Introduction:

In the article by Aronson, the relative bioavailability of 0.75% metronidazole gel with reference to metronidazole solution was evaluated in a single dose randomized crossover study in ten of the patients who completed the efficacy portion of the study.

63/0001

Table 3

PLASMA METRONIDAZOLE

Day 44

<u>Subject No.</u>	<u>Gender</u>	<u>Plasma Metronidazole ng/ml</u>
	M	58
	F	40
	F	40
	M	44
	M	44
	M	44
	F	31
	F	33
	F	30
	F	30
	F	22
	F	N.D.
	F	24
	F	29
	M	25
	F	26
	F	N.D.
	F	20
	F	N.D.
	F	N.D.
	F	N.D.
	F	31
	F	N.D.
	M	22

N.D. = Non detectable (< 20 ng/ml)

Individual Radioactivity Data
Study ICP 63/0003

63/0003

RECOVERY OF RADIOACTIVITY (% DOSE)

GROUP 1 INTACT SKIN

	Mean
Urine	1.32 ± 0.71
Faeces	0.09 ± 0.15
Q-Tips	94.25 ± 3.74
Skin Scraps	0.98 ± 0.81
Total	96.64 ± 2.81

* Excluded from calculations.

#14 Portion of ^{applied} dose dislodged, hence excluded

63/0003

RECOVERY OF RADIOACTIVITY (% DOSE)

GROUP II STRIPPED SKIN

	Mean
Urine	^{AA} 1.37 ± 0.9 3.40 ± 5.4
Faeces	^{AA} 0.18 ± 0.2 0.63 ± 1.2
Q-Tips	93.17 ± 6.9
Skin Strips	0.40 ± 0.3
TOTAL	97.61 ± 2.4

^A Excluded from calculations, because portions of dose dislodged.

^{AA} Mean excretion (% Dose) obtained when subject 4 data excluded.

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OVERALL RECOVERY OF RADIOACTIVITY (% DOSE)

Subject No.								
Urine	0.29	1.61	1.07	15.61	0.75	1.38	0.99	0.73
Faeces	0.00	0.17	0.11	3.35	0.07	0.12	0.00	0.08
Q-Tips	36.28	92.75	94.4	79.16	94.93	93.18	91.92	100.24
Skin Strips	0.17	0.43	0.42	0.24	0.15	0.32	1.77	0.14
TOTAL	36.74	94.96	96.00	98.36	95.90	95.0	94.68	101.19

* Data not used in estimation of mean recoveries of radioactivity.

Contd./...

63/0003

OVERALL RECOVERY OF RADIOACTIVITY (X DOSE)

Subject No.	Mean
Urine	AA 1.34 ± 0.75 2.36 ± 3.9
Faeces	AA 0.13 ± 0.2 0.36 ± 0.9
Q-Tips	93.71 ± 5.3
Skin Strips	0.69 ± 0.7
TOTAL	97.12 ± 2.5

* Data not used in estimation of mean recoveries of radioactivity.

AA Mean excretion (X Dose) obtained when Subject No. 4 data excluded.

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P. 20/100

6.D. Analytical Methods

Table 6.D In Vivo Analytical Methods Summary

Study Number	Submission Date	Biologic Fluid	Method	Sensitivity of Method / Range	Specificity (parent / metabolites)
Pivotal					
Original report DL-6027-9620		Plasma		µg/mL	metronidazole
Supportive					
Original report ICP 63/0003		Plasma Urine Feces Skin tape stripping			¹⁴ C-metronidazole
Original report ICP 63/0001.		Plasma	Not described	Range: not reported LLQ: µg/mL	metronidazole
Literature					
Nielsen. <i>Br J Dermatol.</i> 1983;108: 327-332.		Plasma	HPLC	Range: not reported LLQ: 20 ng/mL	
Aronson et al. <i>Drug Intell Clin Pharm.</i> 1987; 12:346-351.		Serum	HPLC	Range: 25-2000 ng/mL LLQ: 25 ng/mL	metronidazole metronidazole 1-acetic acid hydroxymetronidazole