CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-789

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA Number:	21-789
Stamped Receipt Date(s):	August 24th, 2004 and, October 22nd, 2004
Brand Name:	*Proposed Trade name, MetroGel, 1% was submitted on February 14th, 2005. It is currently being reviewed by the Division of Medication Errors and Technical Support (DMETS)*
Generic Name:	Metronidazole Gel 1%
Reviewer:	Abimbola Adebowale Ph.D.
Acting Team Leader:	Ray Baweja Ph.D.
OCPB Division:	DPE III
ORM division:	HFD-540
Applicant:	Dow Pharmaceutical Sciences, Petaluma, CA 94954-11269
Relevant IND(s):	64,397
Submission Type; Code:	505 (b)(2); 3S (Reference listed drug product is Noritate®)
Formulation; Strength(s):	Gel; 1 %
Indication:	Inflammatory lesions [redacted] of rosacea.

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1. Executive Summary

This application is a 505 (b) (2) application for a new topical dosage form of metronidazole for the treatment of inflammatory lesions and erythema of rosacea. The new dosage form is a 1% Metronidazole Gel with an intended dosing of once daily application. The reference listed drug is a 1% Metronidazole cream, Noritate® Cream, approved under NDA number 20-743 (Dermik Laboratories, Inc.) with once daily application. The applicant stated that their product has not been marketed inside or outside the United States.

Metronidazole is a member of the imidazole class of anti-bacterial agents and it is classified as an antiprotozoal and anti-bacterial agent. It is currently used in several approved prescription products indicated for the treatment of rosacea. These products include MetroGel® 0.75% (metronidazole 0.75%), MetroCream® 0.75% (metronidazole 0.75%), MetroLotion® 0.75% (metronidazole 0.75%), and Noritate®Cream, 1% (metronidazole 1%). All topical treatments for rosacea (with the exception of Noritate®Cream, 1%) are currently approved for twice daily dosing. In addition to topical products, oral dosage forms of metronidazole are also currently marketed for the treatment of rosacea.

In this NDA, Metronidazole Gel 1% has been clinically evaluated in six clinical studies. Four of these studies were phase 1 studies (a 21-day cumulative dermal irritation study, a contact sensitization (RIPT) study, a phototoxicity study, and a photoallergy study). One of these studies was a phase 2 absorption study and one was a pivotal phase 3 controlled trial using Noritate®Cream, 1% as the reference drug. In addition, the applicant referenced two study reports for currently marketed topical metronidazole formulations to support the clinical pharmacology and biopharmaceutics component of this NDA.

1.1 Recommendation (s):

Recommendation on the acceptability of the data:

The Clinical Pharmacology and Biopharmaceutics data submitted on the topical application of metronidazole gel 1% demonstrated that its systemic exposure in patients with rosacea was minimal. This is because the systemic exposure was less than 1 % of the value reported for a single 250 mg oral dose of metronidazole. In addition, the systemic exposure was within the range of the systemic exposure obtained in currently marketed topical formulations of metronidazole including, the RLD, Noritate cream containing metronidazole 1% in healthy volunteers. The applicant has met the requirements outlined in 21 CFR 320 and, the information included in the application is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. We recommend the following labeling changes:

Recommendations on labeling:

The clinical pharmacology section of the draft label should be revised as proposed below.

Reviewer's proposed label changes (strikethroughs are deletions, bolded italics are additions):

Pharmacokinetics: ~~[redacted]~~ ***T***opical administration of a one gram dose of METROGEL ® (metronidazole) Gel, 1% to the face of 13 patients with moderate to severe rosacea ***once daily for 7 days resulted in*** ~~[redacted]~~ ~~[redacted]~~ ***a*** mean ± SD C_{max} of metronidazole ~~[redacted]~~ ***of*** ~~[redacted]~~ ***32± 9 ng/mL.*** ~~[redacted]~~

[redacted] The [redacted] mean ± *SD AUC(0-24)* [redacted] *was* [redacted] *595± 154* [redacted] *ng*hr/mL. The mean C_{max} and AUC (0-24) are less than 1% of the value reported for a single 250 mg oral dose of metronidazole.* The time to maximum plasma concentration (T_{max}) [redacted] was 6-10 hours after topical application.

The remainder of the label, including the drug-drug interaction section was taken verbatim from the label of the RLD product's label (Noritate Cream), and is acceptable from a clinical pharmacology perspective.

1.2 **Phase IV Commitments:**
None were identified

1.3 **Summary of Important Clinical Pharmacology and Biopharmaceutics Findings**

The applicant conducted a single-center, open-label, multiple-dose, study to assess the absorption and safety of metronidazole gel 1% under maximal exposure conditions in 13 patients with moderate to severe rosacea (Study No. 0215-R3.C-04-02). Inserted below are the PK parameters for metronidazole and 2-hydroxymetronidazole:

Table 7: Summary of PK Parameters for Metronidazole and Hydroxymetronidazole

PK Parameter	*N*	*Mean*	*STD*	*Range*
Metronidazole				
Cmin (ng/mL)	13	12.38	4.55	5.81 – 19.37
Cmax (ng/mL)	13	32.05	8.52	17.11 – 44.74
Tmax	13	7.93	1.47	5.92 – 10.00
AUC (0-24) (ng*hr/mL)	13	595.43	154.01	318.36 – 801.66
Hydroxymetronidazole				
Cmin (ng/mL)	13	10.96	4.71	6.36 - 21.40
Cmax (ng/mL)	13	16.86	5.72	11.31 – 26.89
Tmax	13	12.65	4.96	6.05 – 24.13
AUC (0-24) (ng*hr/mL)	13	354.74	116.73	236.81 – 559.09

This study demonstrated that the plasma levels of metronidazole were quantifiable following repeated topical application of Metronidazole Gel 1% to patients with moderate to severe rosacea. In addition, despite the maximal exposure conditions of this study, the mean Cmax and range of Tmax for metronidazole observed in this 7-day study were comparable to that reported for the reference listed drug product, Noritate cream, 1% following a single application to healthy subjects without rosacea. Following the application of 1g metronidazole cream, 1% (Noritate ®) to the face of 16 healthy volunteers in a study previously conducted for that NDA

(#20-743), concentrations of metronidazole were detected in the plasma of 7 of the 16 volunteers in the study. The mean (± SD) C_{max} of metronidazole was 27.6 ± 7.3 ng/mL. The time to maximum plasma concentration (T_{max}) in the volunteers with detectable metronidazole was 8-12 hours after topical application (Noritate® PI).

In addition, two pharmacokinetic study reports obtained from Galderma through Letters of Authorization [(Study No. CR.U9429 for Metrocreme Topical Cream 0.75 % and Metronidazole lotion, 0.75%) in adult healthy volunteers and, (Study No. MAR-10124 for Metrogel, 0.75% formulation) in patients with rosacea], were referenced in support of this NDA for the 1% gel dosage form.

The data from these referenced study reports also indicated that the systemic exposure of metronidazole, 1 % gel was comparable to that of currently marketed topical formulations of metronidazole. In addition, the data further indicated that the systemic exposure observed with metronidazole gel 1% is unlikely to be a safety concern given that the maximum plasma concentration for Metronidazole Gel 1% under maximal use conditions (in Study 0215-R3.C-04-02) was 44.74 ng/ml. The mean Cmax obtained (32.05 ng/mL) was less than 1 % of the mean Cmax value reported for a single 250 mg tablet of metronidazole (Flagyl®) in Study No. CR.U9429 (referenced report from NDA 20-531).

The analytical method (HPLC with UV detection) used for the determination of metronidazole and its active metabolite, 2-hydroxy methyl metronidazole in serum was validated and found to be acceptable.

Signatures:

Reviewer:

Abimbola Adebowale, Ph.D.
Clinical Pharmacology and Biopharmaceutics Reviewer
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

Team Leader Concurrence:

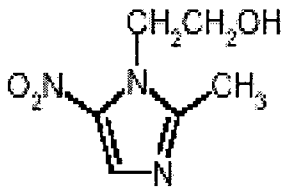
Ray Baweja Ph.D.
Acting Team Leader
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

2. QBR

2.1 General Attributes

Physicochemical Properties of the Drug Substance

Metronidazole 1% gel contains metronidazole, USP. Chemically, metronidazole is 2-methyl-5-nitro-1 H -imidazole-1-ethanol. The molecular formula for metronidazole is $C_6H_9N_3O_3$. Metronidazole has a molecular weight of 171.15. The structural formula of metronidazole is inserted below:



Metronidazole is a white to pale yellow crystalline powder. It is slightly soluble in alcohol and its solubility in water is 10 mg/mL at 20°C.

Therapeutic Indications and Mechanism of Drug Action

The formulation proposed in this application, Metronidazole Gel, 1%, is indicated for the topical treatment of inflammatory lesions [redacted] of rosacea. Rosacea is described as a chronic and recurrent inflammatory dermatological disorder of unknown etiology. It is characterized by inflammatory papules and pustules, facial erythema and telangiectasia. Rosacea is characteristically localized on the face, rarely on the neck, chest, back and scalp. It is believed that the onset of the disorder is usually between the ages of 30 and 50. The applicant stated that early stages of the disease affect women more often than men at a ratio of 3 to 1.

Rosacea is currently treated with both systemic and topical therapies. Drugs used for systemic therapy of rosacea include oral metronidazole (Flagyl®), tetracycline (Minocin®) and isotretinoin (Accutane®). Metronidazole is marketed in different dosage forms for topical application. [redacted]

Proposed Dosage and Route of Administration

Metronidazole 1% gel is to be applied and rubbed in as a thin film once daily to entire affected area(s). Areas to be treated should be cleansed before application of Metronidazole 1% gel.

Reviewer's Comments: Applicant did not provide any timing with regards to when the affected area can be washed after drug application. The medical reviewer (Dr. J. Porres) also confirmed that this was not specified in the clinical trials conducted to support efficacy and safety.

2.2 General Clinical Pharmacology

Q. What were the design features of the clinical pharmacology and clinical studies used to determine safety and efficacy?

The applicant obtained the important safety and efficacy information from the following studies:

Phase 1 studies:

1. Study No. 0215-R3.C-02-02: *A Single Center, Evaluator-Blind Evaluation of the Phototoxicity Potential of Metronidazole Gel(s) 1% and Vehicle(s) Following Topical Application to the Skin of Healthy Subjects*

The sponsor conducted an intra-individual, single-center, evaluator-blind, phase 1 dermal safety study to evaluate the phototoxicity potential of Metronidazole Gel, 1%, and its corresponding vehicle, Metronidazole Gel Vehicle in healthy human subjects. Twenty-seven (27) healthy adult subjects were randomized to receive topical application of Metronidazole Gel, 1%, and Vehicle followed by solar simulated UV irradiation.

2. Study No. 0215-R3.C-03-02: *A Single Center, Evaluator-Blind Evaluation of the Photoallergy Potential of Metronidazole 1% Gel and Vehicle Following Repeated Topical Application to Healthy Subjects*

The sponsor conducted a within subject, single center, evaluator blind, Phase 1 dermal safety study to evaluate the photoallergy potential of Metronidazole Gel, 1%, and its corresponding vehicle, Metronidazole Gel Vehicle in healthy subjects. Photoallergy is photosensitivity mediated by immunologic pathways; the absorption of ultraviolet energy is required for the formation of the hapten or complete antigen. There were 3 phases of this study: induction, rest, and challenge.

3. Study No. 0215-R3.C-05-02: *A Single Center, Evaluator-Blind Evaluation of the Cumulative Irritation Potential of Metronidazole Gel 1%, Vehicle Gel and Control Following Repeated Topical Application to Healthy Subjects*

The sponsor conducted a within subject, single center, evaluator blind, Phase 1 dermal safety study to evaluate the safety in terms of the potential of the test material, Metronidazole Gel, 1%, and its corresponding vehicle, Metronidazole Gel Vehicle, to induce dermal irritation in healthy human subjects as a result of repeated applications. Thirty five (35) healthy adult subjects were randomized to receive Metronidazole Gel, 1%, Metronidazole Gel Vehicle, and 0.2% Sodium lauryl sulfate (positive control), applied under separate occlusive patches on the backs of subjects 3 times per week for three weeks, totaling 21 consecutive days of exposure. Patches were changed every 48 hours (72 hours on weekends).

4. Study No. 0215-R3.C-06-02: *A Single Center, Evaluator-Blind Repeat Insult Patch Test of Metronidazole Gel 1% and Vehicle Following Repeated Topical Applications to Healthy Subjects*

The sponsor conducted a within subject, single center, evaluator blind, Phase 1 dermal safety study to evaluate safety in terms of the potential of the test material, Metronidazole Gel, 1%, and its corresponding vehicle, Metronidazole Gel Vehicle to induce dermal irritation and contact allergy in healthy subjects as a result of repeated applications. The primary objective of this study was to estimate incidence of contact sensitization potential to the test materials. For the three week induction period, irritation scores were tabulated by test article and evaluation day. No formal statistical tests were performed.

Phase II Studies (Clinical Pharmacology Studies):

Study No. 0215-R3.C-04-02: *Absorption of Metronidazole Following Maximum Topical Exposure to Metronidazole Gel 1% in subjects with Moderate to Severe Rosacea.*

The sponsor conducted a single-center, open-label, multiple-dose evaluation to assess the absorption and safety of Metronidazole Gel, 1% under maximal exposure conditions in 13 patients with moderate to severe rosacea. Safety was evaluated by tabulation of adverse events, clinical laboratory (hematology, serum chemistry, and urinalysis) and, by evaluation of the pharmacokinetic profile of metronidazole and its main metabolite, hydroxymetronidazole.

Phase 3 Pivotal Clinical Trial in Patients with Rosacea:

Study No. 0215-R5.C-01-02: *A Multi-Center, Investigator-Blind Clinical Trial to Assess the Safety and Efficacy of Metronidazole Gel, 1% as Compared to Metronidazole Gel Vehicle and Noritate® Cream, 1% in the Treatment of Rosacea*

The sponsor conducted a 10 week, multi-center, randomized, investigator-blind, active-controlled and vehicle-controlled, parallel comparison study in patients with rosacea. A total of 1299 subjects were enrolled (1298 dispensed study medication) into 54 independent study centers. Application of the study medication was made to the face once daily for ten weeks with Metronidazole Gel, 1%, Vehicle gel, or a commercially available metronidazole cream, 1% (Noritate®).®). The disposition of the subjects was as follows: Metronidazole Gel, 1% (N =557 patients), Noritate® Cream, 1% (N = 552 patients) and Metronidazole Gel Vehicle (N =189 patients).

Patients were evaluated for efficacy (inflammatory lesion counts, investigator's global severity score, erythema severity score) and, safety (adverse events and cutaneous signs and symptoms of irritation: dryness, scaling, pruritus, and stinging/burning) at baseline and at Weeks 2, 4, 7 and 10 (or early termination).

This reviewer reviewed the Phase 2 study. The medical reviewer is currently reviewing the Phase 1 and 3 studies.

Q. What is the basis of selecting the clinical or pharmacodynamic response endpoints?

Efficacy assessments were based on blinded investigator assessments of the signs and symptoms of rosacea. The primary efficacy variables were: (1) the percent reduction from baseline in inflammatory lesions (papules, pustules and nodules) at Week 10; and (2) the proportion of subjects rated as successes (clear or almost clear, a score of 0 or 1) in the dichotomized Investigator's Global Severity Score at Week 10, which assessed the severity of erythema and number of inflammatory lesions (see table below).

Table 2.7.3.1.1 Investigator's Global Severity Score

	Grade	Score	Clinical Description
Success	Clear	0	No inflammatory lesions present, no erythema or at most very mild erythema
	Almost Clear	1	Very mild erythema present, very few small papules/pustules
Failure	Mild	2	Mild erythema, several small papules/pustules
	Moderate	3	Moderate erythema, several small or large papules/pustules and up to two nodules
	Severe	4	Severe erythema, numerous small and/or large papules/pustules may be several nodules

Q. What are the characteristics of the exposure-response relationships for efficacy?

The sponsor did not characterize the exposure-response relationships for efficacy for metronidazole gel 1% in this submission because only one strength is being developed and proposed. For dose regimen selection, the applicant stated that the reference listed drug product, Noritate™ Cream, 1%, is a 1% metronidazole formulation labeled for once-daily application. Since Metronidazole Gel, 1% is also a 1% formulation, the once daily application was considered an appropriate test dose.

Q. What are the characteristics of the exposure-response relationships for safety?

The sponsor did not characterize the exposure-response relationships for safety for metronidazole gel 1% in this submission.

Q. What is the systemic exposure of metronidazole 1 % gel following single or multiple dosing?

The systemic exposure of metronidazole was demonstrated to be quantifiable following repeated topical application of Metronidazole Gel 1% to patients with moderate to severe rosacea.

The applicant conducted a single-center study (Study No.0215-R3.C-04-02) designed to characterize the systemic absorption of Metronidazole Gel 1% under maximal exposure using daily topical applications of 1 g/day for 7 days to the face of subjects with moderate to severe rosacea. All subjects had quantifiable concentrations of metronidazole and its active metabolite (Hydroxymetronidazole) on days 2 to 7. This is shown in Figures 1 and 2 inserted below:

Figure 1: Individual and Mean Metronidazole Concentration Levels (ng/mL)

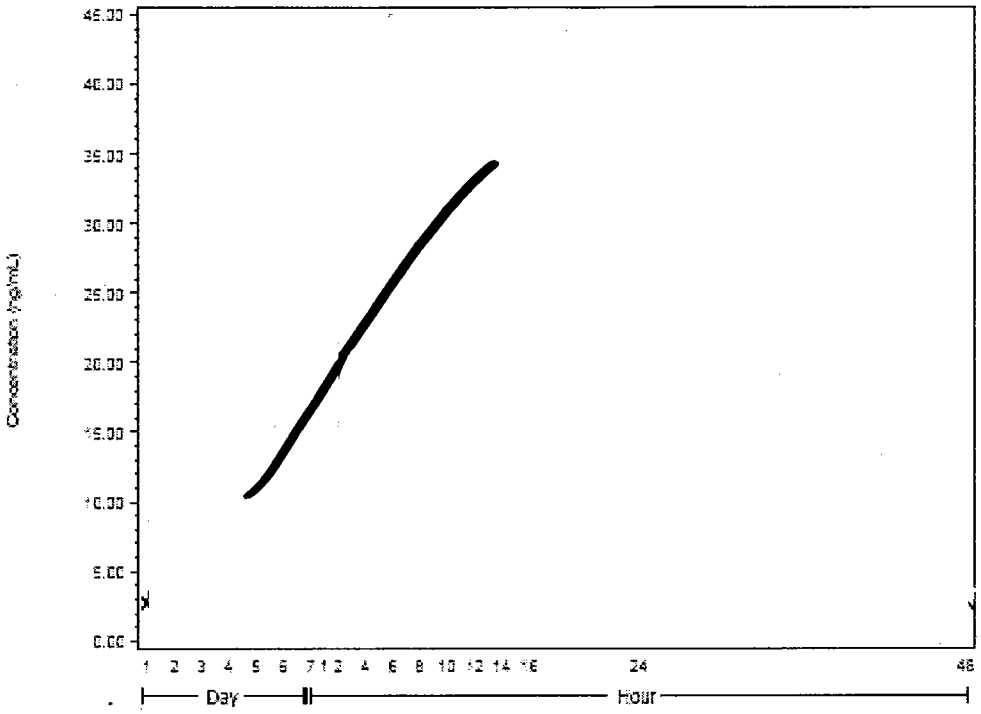


Figure 2: Individual and Mean Hydroxymetronidazole Concentration Levels (ng/mL)

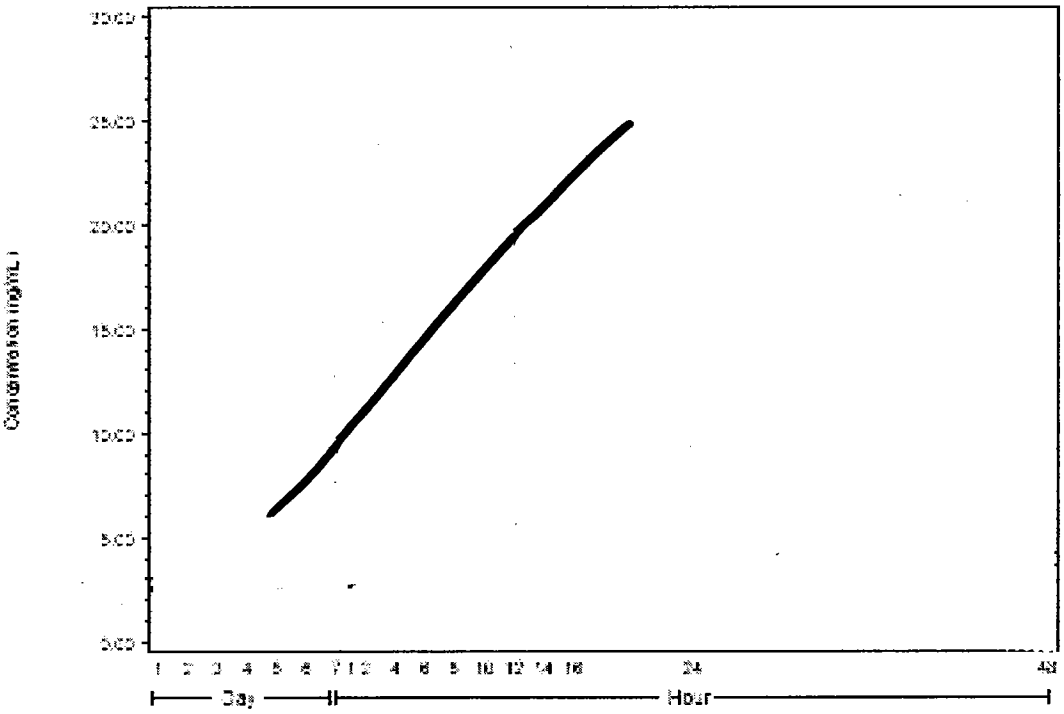


Figure 1: Individual and Mean Metronidazole Concentration Levels (ng/mL)

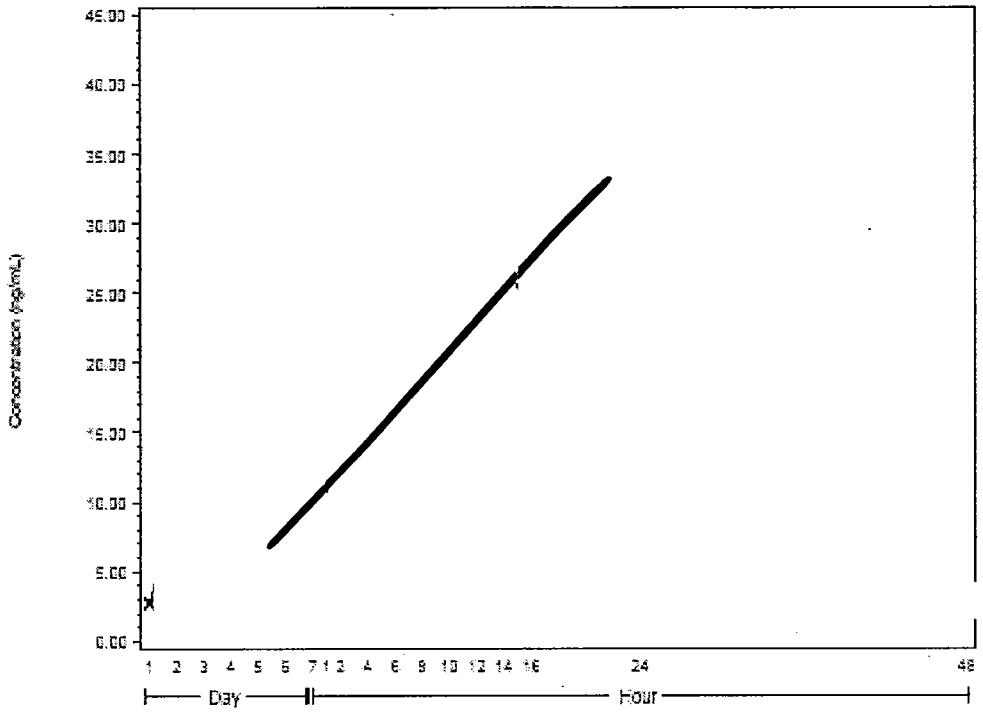
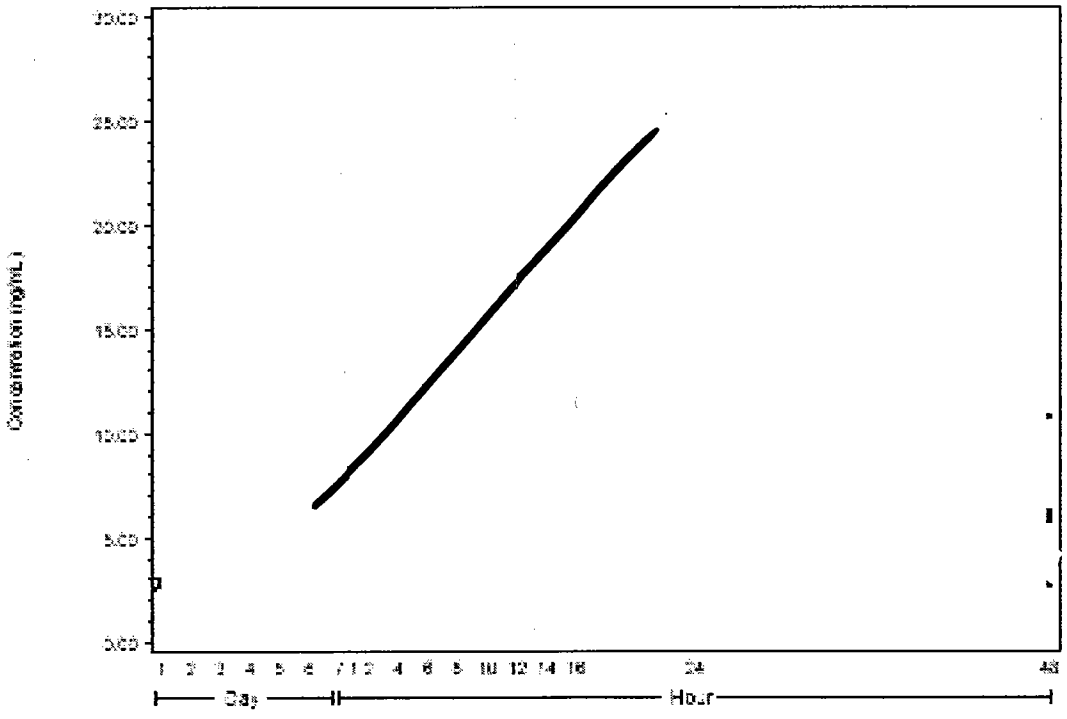


Figure 2: Individual and Mean Hydroxymetronidazole Concentration Levels (ng/mL)



The data in Figure 1 above indicates that based on the trough plasma concentrations metronidazole was at steady state after 4 days of dosing.

Reviewer's Comments: The plasma concentrations in the graph obtained on Day 1 (hour 0), some on day 2, 3, 4, and Day 7 (hour 0 and 48) were below the LOQ and may not be accurate.

The pharmacokinetic parameters obtained for metronidazole and 2-hydroxymetronidazole are shown in the table inserted below:

Table 7: Summary of PK Parameters for Metronidazole and Hydroxymetronidazole
(obtained on Day 7, the last day of dosing)

Concentration	N	Mean	STD	Range
Metronidazole				
Cmin (ng/mL)	13	12.38	4.55	5.81 – 19.37
Cmax (ng/mL)	13	32.05	8.52	17.11 – 44.74
Tmax (hr)	13	7.93	1.47	5.92 – 10.00
AUC $_{(0\text{-}24)}$ (ng*hr/mL)	13	595.43	154.01	318.36 – 801.66
Hydroxymetronidazole				
Cmin (ng/mL)	13	10.96	4.71	6.36 - 21.40
Cmax (ng/mL)	13	16.86	5.72	11.31 – 26.89
Tmax (hr)	13	12.65	4.96	6.05 – 24.13
AUC $_{(0\text{-}24)}$ (ng*hr/mL)	13	354.74	116.73	236.81 – 559.09

Q. How does the systemic exposure of metronidazole from the 1% gel formulation compare to that of the currently marketed topical and oral formulations?

The systemic exposure of Metronidazole Gel, 1%, observed in the maximal exposure study in patients with rosacea was similar to that reported following the application of 1g metronidazole cream, 1% (Noritate®) to the face of 16 healthy volunteers in a study previously conducted for that NDA (#20-743). Low concentrations of metronidazole were detected in the plasma of 7 of the 16 volunteers in the study. The mean (± SD) C_{max} of metronidazole was 27.6 ± 7.3 ng/mL. The time to maximum plasma concentration (T_{max}) in the volunteers with detectable metronidazole was 8-12 hours after topical application to the face for 1 day (Noritate® PI).

In addition, this systemic exposure observed with metronidazole gel 1% is unlikely to be a safety concern given that the maximum plasma level for Metronidazole Gel 1% under maximal use conditions (in Study 0215-R3.C-04-02) was 44.74 ng/ml. The mean Cmax was 32.05 ng/ml which is less than 1 % of the value reported for a single 250 mg tablet of metronidazole (Flagyl®) (7248 ng/ml) in Study No. CR.U9429 (referenced report from NDA 20-531).

*Reviewer's Comments: The relative bioavailability based on the comparison of the mean Cmax (32.05 ng/ml) and AUC (595.43 ng*hr/mL) obtained after topical application of 10 mg of*

*metronidazole to that obtained following a single 250 mg tablet of metronidazole (mean Cmax = 7,248 ng/ml and mean AUC = 67,207 ng*hr/mL),was 11 % and 22 % respectively.*

Q. Were the active moieties in plasma appropriately identified and measured?
Yes, see Section 2.6

2.3. Intrinsic Factors

Q. How does the systemic exposure change with various intrinsic factors?

The applicant did not evaluate the effect of any intrinsic factors on the systemic exposure of metronidazole gel, 1%.

2.4. Extrinsic Factors

Q. How does the systemic exposure change with various extrinsic factors?

The applicant did not evaluate the effects of any new drug-drug interactions on metronidazole exposure when applied as the 1 % gel. However, they did include wording on the possible interaction with anticoagulants in their label. This wording is exactly the same as that of approved Noritate cream (the RLD) and will not be reviewed again. The proposed label wording is inserted below

> **Drug Interaction:** Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin, resulting in a prolongation of prothrombin time. Drug interactions should be kept in mind when Metronidazole 1% gel is prescribed for patients who are receiving anticoagulant treatment, although they are less likely to occur with topical metronidazole administration because of low absorption.

2.5. General Biopharmaceutics

Overview of Biopharmaceutics

Physicochemical Properties of the Metronidazole gel 1 %:

Metronidazole Gel 1% is an aqueous gel; each gram contains 10 mg of metronidazole, USP in a base of purified water, betadex, niacinamide, edetate disodium, methylparaben, propylparaben, phenoxyethanol, propylene glycol, and hydroxyethyl cellulose [redacted] The applicant stated that the gel is essentially clear, colorless to pale yellow, with a pH around 5.5 and viscosity around 1800 to 2600 cps.

Q. What is the in vivo relationship between the to-be-marketed formulation and the pivotal clinical trial formulation(s)?

The applicant stated that there was no difference between the clinical formulations and the proposed commercial formulation. The quantitative composition of the proposed commercial formulation is listed in the table below:

Table 2.3.P.1.1 Quantitative Composition of Metronidazole Gel, 1%

Ingredients	Function	Theoretical Weight (mg/g)	Theoretical Percentage (w/w)
Metronidazole, USP			
Betadex, NF			
Niacinamide, USP			
Edetate Disodium, USP			
Methylparaben, NF			
Propylparaben, NF			
Phenoxyethanol, BP/EP			
Propylene Glycol, USP			
Hydroxyethyl Cellulose, NF,			
Purified Water, USP			
Total			

2.6. Analytical

Q. Were the analytical methods used for the determination of metronidazole and hydroxymetronidazole (its active metabolite) in biological fluids validated?

The analytical method (HPLC with UV detection) used for the determination of metronidazole and its active metabolite, hydroxymetronidazole in serum was validated and found to be acceptable (see table below).

Compound	Metronidazole	2-hydroxymethyl metronidazole
Accuracy		
Within-Day	97.4% to 98.4 %	95.7 % to 103.1 %
Between-Day	97.6 % to 100.7 %	97.3 % to 102.5 %
Precision (CV %)		
Within-Day	1.2 to 2.1 %	1.0 to 4.9 %
Between-Day	2.9 to 6.6 %	2.3 to 5.9 %
Standard Curve range	5.51 to 220 ng/mL (r> 0.99)	5.63 to 225 ng/mL (r > 0.99)
Sensitivity	5.51 ng/mL	5.63 ng/mL

3. Labeling Recommendation:

Applicant's proposed labeling:

CLINICAL PHARMACOLOGY

Pharmacokinetics: Biovailability studies on the topical administration of a one gram dose of **METRONIDAZOLE 1% GEL** to the face of 13 patients with moderate to severe rosacea

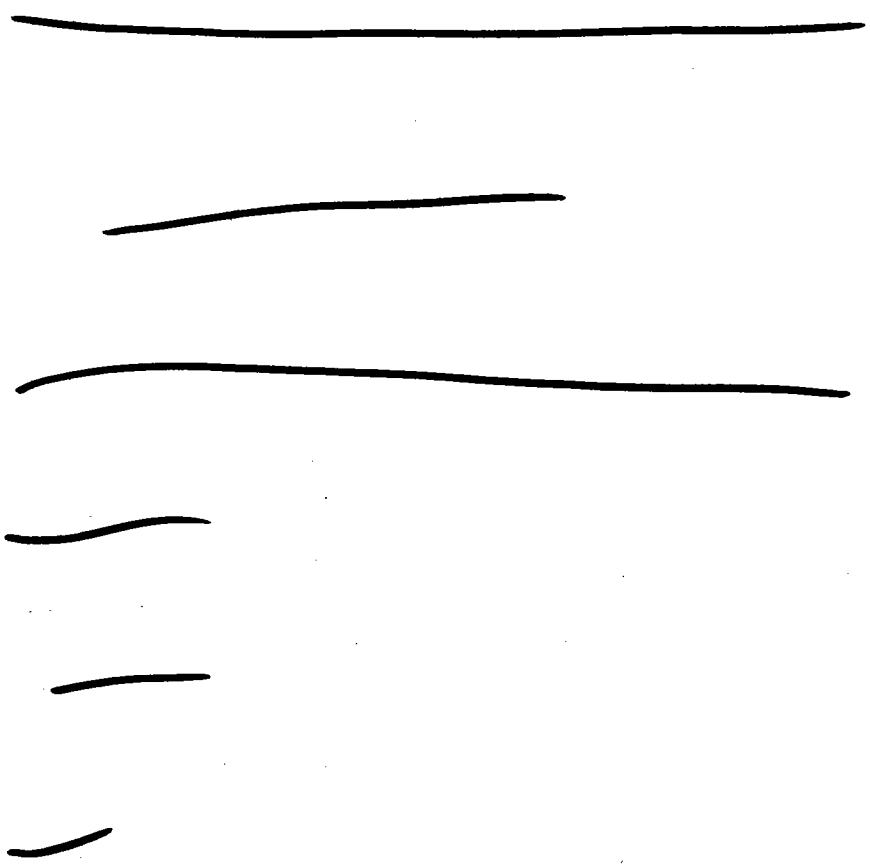
4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

__✓__ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 1



4.3. Individual Study Reviews

Study No. **0215-R3.C-04-02**: Absorption Study in Patients with Rosacea

Title of Study:
Absorption of Metronidazole Following Maximum Topical Exposure to Metronidazole Gel 1% in Subjects with Moderate to Severe Rosacea
Investigators:
Karl R. Beutner, MD, PhD
Study Centers:
Solano Clinical Research, A Division of Dow Pharmaceutical Sciences, 127 Hospital Drive, #202, Vallejo, CA 94589
Studied period (years): October 7, 2002 to November 9, 2002
Phase of Development: 2
Objectives:
The objective of this study was to investigate the absorption and safety of Metronidazole Gel 1% following multiple (daily) applications in the subjects with moderate to severe rosacea.

Methodology:
Single center, open label, multiple dose study
Diagnosis and main criteria for inclusion:
Male or female subjects, 18 years of age and older, with moderate to severe rosacea, defined as having 8 to 50 inflammatory lesions (combined papules and pustules on the face, but no more than 2 nodules) and erythema with a severity score greater than or equal to 2 (i.e. moderate to severe) on a severity scale of 0 to 3 on at least one of the affected areas.
Erythema Severity Score

Score	Clinical Description
0 None	No redness present
1 Mild	Slight pinkness
2 Moderate	Definite redness, easily recognized
3 Severe	Marked erythema;fiery red

Number of subjects (planned and analyzed):
Twelve subjects were planned and the study enrolled 13 subjects. All 13 subjects were included in all analyses. One additional subject was enrolled into the study to ensure that data would be collected for 12 evaluable subjects. The enrollment of the additional subject was reported to the IRB.

Table 2: Subject Demographic and Baseline Characteristics

Number of Subjects	13
Age (Years)	
Mean	54.46
STD	13.23
Range	31.0 - 84.0
Gender	
Male	4 (31%)
Female	9 (69%)
Race	
Caucasian	12 (92%)
African American	0 (0%)
Hispanic	1 (8%)
Asian	0 (0%)
Other[a]	0 (0%)
Height (in)	
Mean	67.23
STD	4.12
Range	59.0 - 73.0
Weight (lb)	
Mean	175.23
STD	25.68
Range	125.0 - 204.0

Total Papule Count	
Mean	13.85
STD	5.58
Range	8.0 - 25.0
Total Pustule Count	
Mean	1.31
STD	2.84
Range	0.0 - 10.0
Total Nodule Count	
Mean	0.08
STD	0.28
Range	0.0 - 1.0
Total Erythema Score	
Mean	7.85
STD	2.27
Range	6.0 - 14.0

Reviewer's Comments: The efficacy measurements used to define moderate to severe rosacea were similar to those used in the Phase 3 trials. The only difference was that in the pivotal Phase 3 trial the inclusion criteria also included the Investigator's Global Severity score which has the erythema severity score included within it.

Test product, dose and mode of administration:
Metronidazole Gel 1% (Batch Number: 755), 1.0 ± 0.1 grams per application, applied topically to the face. Applicant stated that all doses were administered by the clinical personnel for seven days between the hours of 8:00 AM and 10:00 AM, under the supervision of the Investigator. *Applicant stated that Subjects 2, 6, 8 and 9 each had one dose during the course of the study which fell below the 1.0 ± 0.1 gram weighed dosage specification.*

Duration of Treatment:
Once daily for 7 days

Rationale for Selection of doses in the Study:
A once-daily application of the study drug was chosen based on the intended labeling for Metronidazole Gel 1% in the topical treatment of rosacea. The entire face, including the nose and excluding the eyelids and lips, was treated. One application consisted of an average of 1.0 gram of study drug determined by weighing to be within a range of 0.9 g to 1.1g, and the application was selected based on surface area of the face. It is estimated that this area equals about 950-1200 cm^2 and, to cover this area entirely, approximately 1.0g ± 0.1g is needed.

Pharmacokinetic Sampling:
Blood samples (5-7 mL) were collected at Baseline (Day 1) and on Days 2 through 7 prior to dosing to determine trough-levels (C_{min}) of metronidazole and hydroxymetronidazole. After the final dose (Day 7), blood samples were collected at 1, 2, 4, 6, 8, 10, 12, 14, 16, 24 (day 8), and 48 (day 9) hours post dosing.

The samples were allowed to sit for 10 to 20 minutes after drawing to allow the blood to clot. After that time, the samples were [redacted] The serum was aliquotted into two plastic vials.

Analytical Methods:

Serum samples were analyzed for concentrations of metronidazole and the active metabolite 2-hydroxymetronidazole using a [redacted] HPLC with UV detection @ 324 nm. Drug concentration data were provided by the bioanalytical laboratory using quantitation limits of 5.51 ng/mL for metronidazole and 5.63 ng/mL for hydroxymetronidazole. For the purposes of analysis, concentration levels, which were undetected, were set to half the quantitation limit (2.755 ng/mL for metronidazole and 2.815 ng/mL for hydroxymetronidazole).

Reviewer's Comments: This imputation of the data only affected the 48 hour samples. The applicant provided the analysis with and without the 48 hour sample to allow for an evaluation of the effect of the imputation on the data analysis.

Analytical Method Validation:

Compound	Metronidazole	2-hydroxymetronidazole
Internal Standard	Tinidazole	Tinidazole
Accuracy **Within-day** **Between-day**	 97.4% to 98.4 % 97.6 % to 100.7 %	 95.7 % to 103.1 % 97.3 % to 102.5 %
Precision **Within-day** **Between-day**	 1.2 to 2.1 % 2.9 to 6.6 %	 1.0 to 4.9 % 2.3 to 5.9 %
Linearity	5.51 to 220 ng/mL (r> 0.99)	5.63 to 225 ng/mL (r > 0.99)
LOQ	5.51 ng/mL (CV% for N = 9 was 8.0 % and Relative Accuracy was 98.6 %)	5.63 ng/mL (CV% for N = 9 was 7.9 % and Relative Accuracy was 97.3 %)
Selectivity	No interferences were observed at the retention times of interest	
Recovery	44.8 % to 57.9 %	33.1 % to 43.0 %
Stability	Stable (< 11 % degradation) for at least 8 weeks when stored @ -20 °C and -70 °C and over 3 freeze-thaw cycles	
Conclusion	Method Validation is acceptable	

Pharmacokinetic Analysis:

C_{min}, C_{max}, T_{max}, and $AUC_{(0-24)}$ were calculated for each subject using plasma concentrations from Day 7, Hour 0 through Day 7, Hour 48 for metronidazole and its metabolite, hydroxymetronidazole.

Statistical Methods:

All statistical processing was performed using SAS® Version 6.12 or later. The measurements/concentrations of metronidazole and hydroxymetronidazole in the serum were calculated by subject to determine AUC_{0-24} hours, T_{max}, and C_{max}. Mean, standard deviation, and percent CV were calculated for each of these pharmacokinetic parameters. The post-dose and baseline levels of metronidazole and hydroxymetronidazole were compared. A repeated measures analysis of variance was conducted on the concentrations on Day 1 (Baseline) to Day

7, Hour 0 as well as on Day 7, Hour 0 to Day 7, Hour 48 for both metronidazole and hydroxymetronidazole. Paired t-tests were conducted at each timepoint to examine if there was a statistically significant post-dose change in the concentrations of metronidazole and hydroxymetronidazole, each compared to Baseline. The results of the paired t-tests were significant at the 0.05 level of significance only if the overall p-value from the repeated measures analysis of variance was significant at the 0.05 level of significance.

Pharmacokinetic Results:

Plasma Concentrations: All subjects had quantifiable levels of metronidazole and its active metabolite (hydroxymetronidazole)

Table 3: Summary of Plasma Concentrations for Metronidazole and Hydroxymetronidazole (ng/ml) (n = 13) (prior to dosing-Cmin)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7, Hour 0
Metronidazole							
Mean	2.76	9.27	8.27	9.26	12.86	12.46	12.66
STD	0.00	3.16	4.60	3.60	3.11	3.03	4.86
Range	2.8-2.8	2.8-13.2	2.8-16.8	2.8-17.3	7.3-18.9	7.7-16.8	2.8-20.9
Hydroxymetronidazole							
Mean	2.82	8.06	10.54	10.49	11.95	13.34	12.64
STD	0.00	3.64	5.55	5.07	4.85	4.97	4.72
Range	2.8-2.8	2.8-15.9	2.8-26.8	2.8-18.3	6.1-20.7	6.6-23.1	7.0-22.5

Reviewer's Comments: Trough concentrations in table above indicate that SS was achieved by Day 5.

Table 4: Summary of Plasma Concentrations for Metronidazole andHydroxymetronidazole (ng/ml) (Day 7, 1-48 hr sampling time)

	1	2	4	6	8	10	12	14	16	24	48
Metronidazole											
Mean	16.46	21.43	28.03	30.61	31.32	30.07	27.86	26.55	24.53	16.56	2.76
STD	5.26	6.65	7.72	8.10	8.32	7.19	7.16	6.98	6.52	4.54	0.00
Range	5.6-21.9	7.7-29.8	14.0-42.8	15.7-44.7	17.0-44.2	17.1-39.8	15.8-37.0	14.5-35.9	13.3-32.4	8.7-22.8	2.8-2.8
Hydroxymetronidazole											
Mean	11.81	12.30	13.54	14.85	15.69	15.90	15.79	15.30	15.71	13.96	3.92
STD	5.21	4.59	4.62	5.08	4.92	5.24	5.64	5.39	5.76	4.56	2.39
Range	2.8-22.2	6.6-21.8	7.8-21.4	8.1-22.7	10.2-23.0	10.8-24.6	9.7-25.3	10.3-25.6	10.2-26.9	9.3-22.3	2.8-10.8

A summary of the PK parameters are inserted in the table below.

Table 7: Summary of PK Parameters for Metronidazole and Hydroxymetronidazole
(obtained on Day 7, the last day of dosing)

Concentration	N	Mean	STD	Range
Metronidazole				
Cmin (ng/mL)	13	12.38	4.55	5.81 – 19.37
Cmax (ng/mL)	13	32.05	8.52	17.11 – 44.74
Tmax (hr)	13	7.93	1.47	5.92 – 10.00
AUC $_{(0\text{-}24)}$ (ng*hr/mL)	13	595.43	154.01	318.36 – 801.66
Hydroxymetronidazole				
Cmin (ng/mL)	13	10.96	4.71	6.36 - 21.40
Cmax (ng/mL)	13	16.86	5.72	11.31 – 26.89
Tmax (hr)	13	12.65	4.96	6.05 – 24.13
AUC $_{(0\text{-}24)}$ (ng*hr/mL)	13	354.74	116.73	236.81 – 559.09

Reviewer's Comment: The above table by the applicant was slightly modified by this reviewer. The last column originally had the percent CV in it, this reviewer changed it to the range, since the percent CV will be giving the same information as the SD and the range will be useful in this case for comparison to other currently marketed topical products. In addition the percent CV originally included in the table was just the CV.

Applicant's Safety Conclusions:
Adverse events were reported in 7 of the 13 subjects with a total of 13 adverse events and no serious adverse events. Twelve of the adverse events were classified as mild and one was classified as moderate. The relationship of the adverse events to Metronidazole Gel 1% were as follows: Eight events (62%) were classified as definitely unrelated or unlikely related to study drug. Five events (38%) were reported as possibly related to study drug. None of the adverse events were considered probably related or related to the study drug. Events reported were related to skin and subcutaneous tissue disorders (dry skin, erythema, skin laceration, skin tightness); nervous system disorders [burning sensation NOS (= not otherwise specified, i.e., it cannot be assigned to a more definitive term), dysgeusia];]; blood and lymphatic system disorders (ecchymosis); gastrointestinal disorders (diarrhea NOS, nausea, vomiting NOS); investigations (heart rate irregular); and musculoskeletal and connective tissue disorders (back pain).

Reviewer's Comments: This data is currently being reviewed by the medical reviewer.

Applicant's Conclusion:
On average, the maximum metronidazole concentration was 32.05 ng/mL and the maximum hydroxymetronidazole concentration was 16.86 ng/mL. On average, the observed times of maximum concentration of metronidazole and hydroxymetronidazole were 7.93 hours and 12.65 hours, respectively. This study demonstrates that the levels of metronidazole absorption are minimal following repeated topical application of Metronidazole Gel 1% to patients with

moderate to severe rosacea. The safety profile of this formulation is supported by the fact that the levels observed in this maximal exposure study are similar to those observed in studies with marketed metronidazole formulations (MetroLotion 0.75%, and Noritate® cream, 1% (RLD)) in healthy subjects under minimal exposure conditions. The safety of Metronidazole Gel 1% is further supported given that the maximum plasma level attained under the study conditions, 44.74 ng/ml, is less than 1% of that reported for a single 250 mg oral dose of metronidazole (5.1 (1.7) µg/ml) (Amon I, et al., 19789 [Vagimid®]; Lamp KC, et al., 1999) and 20% of that reported for a single 250 mg tablet of metronidazole (Flagyl®) (217.4 ng/ml) * reported in Study No. CR.U9429 (NDA 20-531).

* Applicant stated that Cmax is a value that was standardized to a dose of 7.5 mg (i.e. the dose of topical gel applied in that NDA) by multiplying the actual mean Cmax (7248 ng/ml) by 7.5/250 mg=217.44 ng/ml.

Reviewer's Comment: The applicant's conclusion above shows a higher value for Cmax obtained from the published literature for the oral tablet (5100 ng/mL) compared to that obtained from their study report (217.4 ng/mL). This is because the latter value was standardized as explained in the footnote above.

*For this NDA, the relative bioavailability (BA) based on the comparison of the mean Cmax (32.05 ng/ml) and AUC (595.43 ng*hr/mL) obtained after topical application of 10 mg of metronidazole to that obtained following a single 250 mg tablet of metronidazole (mean Cmax = 7,248 ng/ml and mean AUC = 67,207 ng*hr/mL), was 11 % and 22 % respectively. The relative BA was calculated as follows: For Cmax = [{(32.05/10)/ (7,248/250)) * 100} = **11 %**] and for AUC = [{(595.43/10) / (67,207/250) * 100} = **22 %**].*

It should be noted that the applicant has proposed to include the 1% value in their label which is based on the comparison of the absolute values, and it appears that this is what has been included in the label for previously marketed topical products.

Summary of Previous Study Reports:

The applicant stated that although these studies were performed with lower concentrations (0.75 %) of metronidazole, the applicant considered the penetration profile to be similar to that of Metronidazole Gel, 1%.

Reviewer's Comments: The study reports for the 0.75 % topical dosage forms provided were already reviewed by OCPB in their respective NDAs and were not reviewed here again. A brief summary of the study reports is provided below because some data from the study was referenced in this NDA.

Inserted below is a table showing the comparisons of PK data across studies for the different currently marketed topical formulations of metronidazole. Please note that the table was slightly modified by deleting some columns from the applicant's original version to allow it to fit on one page. In addition the first two rows which includes the data from this NDA and the PI for the RLD were entered by this reviewer.

NDA # Study/ Protocol#	Product ID/ Batch #	Study Design ,# Subjects Completed (M/F) Healthy Volunteer (HV) Patient (P) (Age: Mean, Range)	Treatment	Mean (SD)Parameters		
				Cmax (ng/mL)	Tmax (hr)	AUC(0-24) ng/mL-h
NDA 21-789 0215-R3.C-04-02 (USA)	***Metronidazole Gel, 1%/Batch 755***	***Open label multiple dose (4M/9F) P (54.46, 31-84)***	***1.0 ± 0.1 g to face qd X 7d***	***32.05 (8.52)***	***7.93 (1.47)***	***595.43 (154.01)***
NDA 20-743 PDR	Noritate ® (Metronidazole Cream 1 %)	Single dose 16 HV	1.0 g to face x 1d	27.6 (7.3)	8-12	Not included in label
NDA 20-531 CR.U9429 [Metrocream]	Metronidazole Cream, 0.75%/ Batch 3D0547	Open label, randomized, four-way crossover, single dose (5M/7F/ (5M/7F) HV (27.8, 24-34) Each of the four treatments in randomized order with a minimum 7-day washout between treatments	1) 1 g metronidazole cream, 0.75%, topically to face x 1d	32.9 (10.6)	10.62 (6.82)	600.0 (185.1)
	Metronidazole Lotion, 0.75%/ Batch HHBZ-3		2) 1 g metronidazole lotion, 0.75%, topically to face x 1d	34.4 (11.4)	9.36 (2.47)	634.1 (213.1)
	Metronidazole Topical Gel (MetroGel®), 0.75%/ Batch HEBD-1		3) 1 g metronidazole gel, 0.75% topically to face x 1d	29.1 (6.7)	8.51 (2.84)	555.6 (124.2)
	Metronidazole Tablet (Flagyl®), 250 mg/ Batch 3F193		4) 250 mg metronidazole tablet po x 1d	7248 (3019)	1.51 (1.39)	67207 (15380)
NDA 19-737 MAR-10124 [MetroGel]	Metronidazole Topical Gel, (MetroGel®), 0.75%/ Batch CPI-2-01025	Randomized, crossover, single dose (5M/5F)/ (5M/5F) P (50.5. 25-74) Each of the treatments in randomized order with a minimum 7-day washout between treatments:	1) 1 g metronidazole gel, 0.75% topically to face x 1d	66 (45.3)	5.98[2]	NA[1]
	Metronidazole Solution Oral 500 mg/100 mL/ Batch 159521		2) 30 mg metronidazole solution, 500 mg/100 mL, po x 1d	850 (50.7)	0.972	7476.1 (35.8)

[1]NA-Accurate estimation of AUC not possible due to less-than-detectable serum concentrations at the majority of time points. [2]Median T_{max} values are presented.

The data in the table above demonstrates that that the levels observed in the maximal exposure study for Metronidazole Gel, 1% were similar to those observed in studies with marketed metronidazole formulations (metronidazole lotion, 0.75% (MetroLotion.), and metronidazole

cream, 1% (Noritate®) in healthy subjects and, Metronidazole gel 0.75 % in patients with rosacea following a single application.

1. Study No. CR.U9429: *Pharmacokinetic/bioavailability evaluation of topically administered metronidazole cream, 0.75% and metronidazole lotion, 0.75% in healthy adult volunteers.*
Inserted below

Table 2.7.2.2.6 Metronidazole and 2-Hydroxymethylmetronidazole range of maximum plasma concentration (N = 12)

(ng/mL)	Topical Metronidazole 0.75% Formulations			Oral Metronidazole
	Lotion	Cream	Gel	
Metronidazole	19.7 - 63.8	14.8 - 54.4	19.1 - 42.7	4270 - 13970
2-OH Methylmetronidazole	BQL* - 17.3	BQL* - 17.5	BQL* - 17.6	626 - 1788

*Below quantifiable limit

Table 2.7.2.2.5 Mean Metronidazole Tlag and Tmax

[mean, (SD)]	Topical Metronidazole 0.75% Formulations			Oral Metronidazole
Parameters	Lotion	Cream	Gel	
T_{lag} (h)	0.99 (0.91)	0.81 (0.44)	0.89 (0.64)	0.09 (0.17)
T_{max} (h)	9.36 (2.47)	10.62 (6.82)	8.51 (2.84)	1.51 (1.39)

Table 2.7.2.2.7 Mean Dose-adjusted Pharmacokinetic Parameters for Metronidazole

[mean, (SD)]	Topical Metronidazole 0.75% Formulations			Oral Metronidazole
Parameters*	Lotion	Cream	Gel	
C_{max} (ng/mL)	34.4 (11.4)	32.9 (10.6)	29.1 (6.7)	217.4 (90.6)
AUC_{24}(ng*hr/mL)	634.1 (213.1)	600.0 (185.1)	555.6 (124.2)	1755.1 (351.7)
AUC_{∞} (ng*hr/mL)	971.1 (433.6)	912.7 (379.7)	814.8 (251.4)	2016.2 (461.4)

*Cmax and AUC were standardized to a dose of 7.5 mg by multiplying the calculated value by 7.5/administered dose

The dose-adjusted metronidazole C_{max}, AUC_{24}, and AUC_{∞} were significantly greater ($p < 0.05$) after the administration of oral tablet as compared to lotion, cream, or gel formulations. No significant difference ($p > 0.05$) in these parameters was found among the three topical formulations.

Table 2.7.2.2.8 Mean Tmax and Dose-Adjusted Cmax for 2- Hydroxymethylmetronidazole

[mean, (SD)]	Topical Metronidazole 0.75% Formulations			Oral Metronidazole
Parameters	Lotion	Cream	Gel	
T_{max} (hr)	17.63 (6.87)	14.83 (6.60)	15.27 (6.24)	8.53 (2.44)
C_{max} (ng/mL)	11.8 (5.9)	10.7 (5.5)	10.8 (5.6)	34.7 (11.7)

For this metabolite, the other pharmacokinetic parameters were not calculated and statistical analysis of C_{max} was not performed due to the occurrence of no quantifiable 2-hydroxymethylmetronidazole serum concentrations in several sets of serum concentration time data from the three topical formulations.

Table 6
Pharmacokinetic Parameters (unadjusted) After Oral Administration of the 250 mg Metronidazole Tablet

	Metronidazole						Hydroxymetronidazole		
Subject	C_{max} (ng/ml)	T_{max} (hr)	AUC_{24} (ng-hr/ml)	AUC_{∞} (ng-hr/ml)	V (l)	λ_z (hr-1)	C_{max} (ng/ml)	T_{max} (hr)	AUC_{24} (ng-hr/ml)
1	8531	0.53	67341	73773	33.12	0.102	1338	8.02	21936
2	4571	3.00	43361	46399	45.47	0.119	1788	8.00	31600
3	11978	0.25	71534	89933	39.93	0.070	693	4.00	14080
4	4632	1.00	45613	55882	63.37	0.071	820	8.00	16228
5	6871	0.50	42572	45403	47.96	0.115	1383	8.17	26075
6	5962	4.07	78302	96476	36.06	0.072	626	12.03	11438
7	8217	1.02	61342	66877	36.05	0.104	1250	5.98	22228
8	6604	1.50	60202	65657	36.13	0.105	1686	12.00	32734
9	5954	1.05	64230	73505	38.52	0.088	1126	8.07	22198
10	13970	0.25	65045	70644	34.46	0.103	1480	8.00	29548
11	4270	4.00	47312	58043	56.23	0.077	876	8.00	16223
12	5411	1.00	55188	63890	46.58	0.084	834	12.03	16132
Mean	**7248**	**1.51**	**58504**	**67207**	**42.82**	**0.092**	**1158**	**8.53**	**21702**
SD	**3019**	**1.39**	**11724**	**15380**	**9.42**	**0.018**	**390**	**2.44**	**7106**
CV (%)	**42**	**91.47**	**20**	**23**	**22.01**	**19.138**	**34**	**28.58**	**33**
Median	**6283**	**1.01**	**60772**	**66267**	**39.22**	**0.095**	**1188**	**8.01**	**22067**

Applicant's Conclusions:
In conclusion, absorption of metronidazole after topical application of a single 1 g dose of the metronidazole 0.75% lotion, cream, or gel formulations (7.5 mg metronidazole), was less complete and more prolonged than after oral administration. The relevance of the differences in metronidazole and 2-hydroxymethylmetronidazole serum concentrations between the topical formulations and the 250 mg oral tablet was shown by the higher frequency of adverse effects after oral metronidazole administration. The rate and extent of metronidazole absorption after topical application of the metronidazole lotion, 0.75% formulation was not significantly different from that seen with the currently marketed metronidazole gel, 0.75% (MetroGel®) or metronidazole cream, 0.75% (MetroCream™).

2. Study No. MAR-10124: *Pharmacokinetic/bioavailability evaluation of topically administered 0.75% metronidazole gel.*

Table 2.7.2.2.10 Mean Cmax and AUC, Median Tmax for Metronidazole

Dosage Form Route of Administration	Parameters Dose	Mean C_{max} (ng/mL)	Median T_{max} (hr)	Mean AUC (ng/hr/mL)
Metronidazole Gel, (MetroGel®) 0.75%Topical	7.5 mg	66	5.98	*
500 mg/100 mL Metronidazole Solution Oral	30 mg	850	0.97	7476.1

*Accurate estimation of AUC not possible due to less-than-detectable serum concentrations at the majority of time points.

It was concluded that minimal absorption of metronidazole occurs following single dose, topical application of metronidazole gel, 0.75%.

In another study performed on metronidazole lotion, 0.75% (MetroLotion.), detectable plasma levels were found in all subjects following the administration of a single 1 g dose to the face of 12 healthy volunteers. The highest concentration seen was 64 ng/ml.

Tabular Summary of the Phase I Clinical Studies

Study ID	**Design Control Type**	**Study & Ctrl Drugs Dose, Route & Regimen**	**# subj by arm entered/completed, Gender, M/F (Median Age Range)**	**Diagnosis Inclusion Criteria**	**Primary Endpoints**
Phase 1 Phototoxicity 0215-R3.C-02-02	Within subject, single center, evaluator-blind, vehicle controlled , phase 1 dermal safety study	Metronidazole Gel, 1% and Metronidazole Gel Vehicle. 50 µL topically to separate sites on back followed by 10x MED* of UVA then 0.5X MED of UVA/UVB ***Duration = 48 hours***	29/29, 8/21 (25.6; 18-62)	Healthy Volunteers Skin type sensitive to normal (I-IV, per protocol)	Assessed skin irritancy on a 6-point scale of 0 (no sign of irritation) to 4 (erythema with edema and blistering).
Phase 1 Photoallergy 0215-R3.C-03-02	Within subject, single center, evaluator-blind, vehicle controlled , phase 1 dermal safety study	Metronidazole Gel, 1% and Metronidazole Gel Vehicle. 200 µL topically (on occlusive patches) to separate sites on back, followed 24hr later by 10x MED of UVA then 0.5X MED of UVA/UVB Twice a week for three weeks. Following a two-week rest a single challenge treatment was performed. ***Duration = 6 weeks***	30/28 10/18 (33.9; 20-53)	Healthy Volunteers Skin type sensitive to normal (I-IV, per protocol)	1)Assessed skin irritancy on a point scale of 0 (no sign of irritation) to 4 (erythema with edema and blistering). 2)Criteria for Photoallergy reaction: i) site reached a Grade 3 or 4 reaction, ii) reaction persisted after removal of patch, iii) reaction reproduced upon challenge
Phase 1 21-Day Cum 0215-R3.C-05-02	Within subject, single center, evaluatorblind, vehicle	Metronidazole Gel, 1%, Metronidazole Gel Vehicle and Sodium lauryl sulfate 0.2%.	35/31 16/19 (27.4; 18-70)	Healthy Volunteers	Assessed skin irritancy on a point scale of 0 (no sign of irritation) to 4 (erythema with edema and

	controlled, phase 1 dermal safety study	200 ∝L topically (on patches) to separate sites on back, 3 times/w x 3 weeks ***Duration = 3 weeks***			blistering).
Phase 1 RIPT 0215-R3.C-06-02	Within subject, single center, evaluator blind, vehicle controlled, phase 1 dermal safety stud	Metronidazole Gel, 1% and Metronidazole Gel Vehicle. 200 ∝L topically (on patches) to separate sites on back, 3 times/wk x 3-wks. Following a two week rest period, treatments were applied to naïve sites for 48hours. ***Duration= 6weeks***	230/215 86/144 (21; 18-60)	Healthy Volunteers	1) Assessed skin irritancy on a 6-point scale of 0 (no sign of irritation) to 4 (erythema with edema and blistering). 2) Criteria for Contact sensitization: i). site reached a Grade 3 or 4 reaction, ii) reaction persisted after removal of patch, iii) reaction reproduced upon rechallenge

* MED = Minimal Erythema Dose

4.4. OCPB Filing form

Office of Clinical Pharmacology and Biopharmaceutics ***New Drug Application Filing and Review Form***			
General Information about the Submission			
	Information		Information
NDA Number	21-789	**Brand Name**	Will be chosen at a later date
OCPB Division (I, II, III)	DPEIII	**Generic Name**	Metronidazole Gel 1%
Medical Division	HFD-540	**Drug Class**	Antiprotozoal and Antibacterial
OCPB Reviewer	Abi Adebowale	**Indication(s)**	Topical treatment of inflammatory lesions [redacted] of Rosacea.
OCPB Team Leader	Ray Baweja	**Dosage Form**	Gel
		Dosing Regimen	Apply and rub in a thin film once daily to entire affected area(s)
Date of Submission, Filing Date	August 27th, 2004 October 27th, 2004	**Route of Administration**	Topical
Mid Cycle Review Date	January 27th, 2005		
Estimated Due Date of OCPB Review	April 15th, 2005	**Sponsor**	Dow Pharmaceutical Sciences
PDUFA Due Date	June 30th, 2005	**Priority Classification**	3S
Division Due Date	May 1st, 2005	**IND Number**	64,397

Clin. Pharm. and Biopharm. Information

Background and Introduction: Metronidazole Gel 1% is an aqueous gel; each gram contains 10 mg of metronidazole in a base of purified water, betadex, niacinamide, edetate disodium, methylparaben, propylparaben, phenoxyethanol, propylene glycol, and hydroxyethyl cellulose [redacted]

Metronidazole is an antimicrobial agent used in several approved prescription products indicated for the treatment of rosacea. These products are MetroGel® 0.75% (metronidazole 0.75%), MetroCream® 0.75% (metronidazole 0.75%), MetroLotion® 0.75% (metronidazole 0.75%), and Noritate® Cream, 1% (metronidazole 1%). The proposed product, Metronidazole Gel 1%, has been developed for the topical treatment of rosacea. Applicant states that this product will provide a non-alcoholic gel dosage form (often preferred by patients with rosacea) in 1% metronidazole strength. In addition to topical products, oral and intravenous dosage forms of metronidazole are currently marketed for treatment of a variety of infectious diseases.

The product proposed in this 505(b) (2) application has been clinically evaluated in six clinical studies. Four of these studies were phase 1 studies; a 21-day cumulative dermal irritation study, a contact sensitization (RIPT) study, a phototoxicity study, and a photoallergy study. One of these studies was a phase 2 absorption study and one was a pivotal phase 3 controlled trial using Noritate® Cream, 1% as the reference drug.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			Submitted to EDR on 10-22-04. Received access on 10-27-04
1. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	X	1		Study CR.U9429 (conducted to support Metrogel 0.75%) an approved product (supportive)
Patients-				
single dose:				
multiple dose:	X	1		Study No. 0215-R3.C-04-02 (pivotal) and supportive study MAR10124 (using Metrgel 0.75%)
Dose proportionality -				
Fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

renal impairment:				
hepatic impairment:				
PD (HEALTHY OR PATIENTS):				
Phase 1 or 2:				
Phase 3:				
PK/PD (HEALTHY OR PATIENTS):				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
Alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Other (in vitro percutaneous absorption study)				
Chronopharmacokinetics				
Pediatric development plan				
Literature References		**10**		To support ADME. However, since this information was not included in the label it was not reviewed
Total Number of Studies		**1**		

Fileability and QBR comments		
	"X" if yes	Comments Sent request through project manager for applicant to direct me to the location of the assay method for Study 0215-R3.C-04-02. Received on 10-22-04
Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	**NA**	Comments have been sent to firm (or attachment included), FDA letter date if applicable.
QBR questions (key issues to be considered)	What is the maximal systemic exposure or bioavailability of metronidazole following application as a 1% gel to patients with rosacea? What is the exposure-response relationship for efficacy and safety? Do we need a PM consult? ***NO***	
Other comments or information not included above		
Primary reviewer Signature and Date	**Abi Adebowale 03/28/05 (first draft); 05/03/05 (second draft)**	
Secondary reviewer Signature and Date		

CC: NDA 21-789, HFD-850 (P.Lee), HFD-540 (K. Bhatt), HFD-880 (R.Baweja, A. Selen)

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

/s/

Abi Adebowale
5/25/05 05:17:16 PM
BIOPHARMACEUTICS

Raman Baweja
5/25/05 06:01:25 PM
BIOPHARMACEUTICS