CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-789

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-789**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**8/27/04**
PRODUCT:	**Metronidazole 1% Gel**
INTENDED CLINICAL POPULATION:	**Patients with rosacea**
SPONSOR:	**Dow Pharmaceutical Sciences**
DOCUMENTS REVIEWED:	**All**
REVIEW DIVISION:	**Division of Dermatologic and Dental Drug Products (HFD-540)**
PHARM/TOX REVIEWER:	**Norman A. See, Ph.D.**
PHARM/TOX SUPERVISOR:	**Paul Brown, Ph.D.**
DIVISION DIRECTOR:	**Jon Wilkin, M.D.**
PROJECT MANAGER:	**Kalyani Bhatt**

Date of review submission to Division File System (DFS): 3/4/05

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: The product is approvable with respect to nonclinical concerns under a 505(b)(2) application.

B. Recommendation for nonclinical studies: None.

C. Recommendations on labeling: The [redacted] ' section of the draft label should be deleted. The remainder of the label, including the "Pregnancy", "Carcinogenesis, Mutagenesis and Impairment of Fertility", and "Nursing Mothers" sections were lifted verbatim from the label of the RLD product's label (Noritate Cream), and are acceptable with respect to nonclinical issues.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: This is a 505(b)(2) application for a topical metronidazole 1% gel product. The primary basis for approval of the product from a nonclinical perspective is the prior finding of the Agency that a similar product, (Noritate (1% metronidazole) cream, NDA 20-743, Galderma, approved 26-SEP-1997), was safe and effective. Additional evidence of safety was provided by a series of studies conducted with the subject of NDA 21-789 (the current clinical formulation or a very closely related formulation). These studies included a 13-week repeat-dose topical dermal toxicology study conducted with minipigs, as well as assays for potential to induce skin or eye irritation or sensitization. No remarkable toxicity was observed in those studies. The excipients and impurities in the product have been qualified.

B. Pharmacologic activity: The mechanism of action by which metronidazole exerts efficacy against rosacea is unknown.

C. Nonclinical safety issues relevant to clinical use: Metronidazole is a genotoxic carcinogen, and it is unclear if the benefit to be derived from the product in the treatment of rosacea would be sufficient to support approval of a 505(b)(1) application in the current regulatory environment. However, NDA 21-789 is a 505(b)(2) application, so this point is moot. There are no other notable nonclinical safety concerns.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

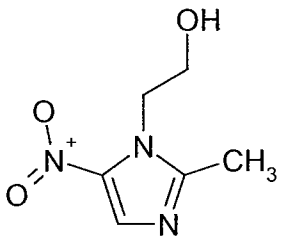
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-789
Review number: 1
Sequence number/date/type of submission: N-000/27-AUG-2004
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Dow Pharmaceutical Sciences
Manufacturer for drug substance: [redacted]

Reviewer name: Norman A. See, Ph.D.
Division name: Division of Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: 16-FEB-2005

Drug:

Trade name: Metronidazole Gel, 1%
Generic name: Metronidazole
Code name: NA
Chemical name: 2-methyl-5-nitroimidazole-1-ethanol
CAS registry number: 443-48-1
Molecular formula/molecular weight: $C_6H_9N_3O_3$/171.16
Structure:



Relevant INDs/NDAs/DMFs: NDA 20-743 (Noritate Cream, Galderma, AP 26-SEP-1997)

Drug class: Antimicrobial agent

Intended clinical population: Patients with rosacea

Clinical formulation:

Clinical formulation (per dosage unit):

Component	Amount (% w/w)
Metronidazole, USP	[redacted]
Betadex, NF	[redacted]
Niacinamide, USP	[redacted]
Edetate Disodium, USP	[redacted]
Methylparaben, NF	[redacted]
Propylparaben, NF Phenoxyethanol, BP/EP Propylene Glycol, USP Hydroxyethyl Cellulose, NF,	[redacted]
Purified Water, USP	[redacted]
Total	100.0

Route of administration: Topical to the skin. The proposed use of the product involves application to areas of the head and neck that are affected by rosacea. This area comprises approximately 4% of the body surface area. The material would be applied once daily for an indefinite period, resulting in chronic exposure to the product. Approximately 2 grams of product may be applied per day to a given patient.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-789 are owned by Dow Pharmaceuticals or are data for which Dow Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 21-789 that Dow Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Dow Pharmaceuticals does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-789.

Studies reviewed within this submission:

1. Sub-chronic (4 weeks) toxicity study by the cutaneous route in the Sprague-Dawley strain of rat of Rozex lotion and Rozex gel containing metronidazole at 0.75% (w/w). Study No. 1.CG.03.SPR.8163.GDL.

2. 13-week dermal toxicity study in rabbits. Study No. 6205-100.

3. A 3-month dermal toxicity study of metronidazole gel (1%) in Hanford minipigs. Study No. 0215-R2.R-07-02.

4. A primary skin irritation study in rabbits with metronidazole gel 1%, study No. 0215-R2.R-01-01 (conducted with a preliminary formulation that contained [redacted]

5. FHSA primary dermal irritation, study No. 0215-R2.R-03-02.

6. Primary skin irritation potential of a metronidazole gel 1%. Study No. 0215-R2.R-04-02.

7. Primary eye irritation potential of metronidazole gel 1%. Study No. 0215-R2.R-05-02.

8. A dermal sensitization study in guinea pigs with metronidazole gel, 1% (maximization design), study. No. 0215-R2.R-02-01.

9. Dermal sensitization of metronidazole gel 1% in guinea pigs - Magnusson-Kligman (ISO) method. Study No. 0215-R2.R-06-02.

Studies not reviewed within this submission: The submission contained a number of photocopies of journal articles that were not specifically summarized in this review because they were judged to add no useful information to the database that was captured in the review.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Metronidazole kills certain species of protozoa and anaerobic bacteria through the mechanism described below. The mechanism through which metronidazole ameliorates rosacea is unknown.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Quoting Goodman's and Gilman's "The Pharmacological Basis of Therapeutics":

> "Metronidazole is a prodrug; it requires reductive activation of the nitro group by susceptible organisms. Its selective toxicity towards anaerobic and microaerophilic pathogens such as the amitochondriate protozoa, *T. vaginalis, E. histolytica*, and *G. lamblia*, and various anaerobic bacteria derives from their energy metabolism, which differs from that of aerobic cells... These organisms, unlike their aerobic counterparts, contain electron transport components such as ferredoxins, small Fe-S proteins that have a sufficiently

> negative redox potential to donate electrons to metronidazole. The single electron transfer forms a highly reactive nitro radical anion that kills susceptible organisms by radical-mediated mechanisms that target DNA and possibly other vital biomolecules".

However, the method by which metronidazole ameliorates rosacea is unknown.

Drug activity related to proposed indication: Metronidazole ameliorates rosacea through an unknown mechanism.

2.6.2.3 Secondary pharmacodynamics

None.

2.6.2.4 Safety pharmacology

Neurological effects: No data were submitted; this is a 505(b)(2) application that relies upon a prior finding of the Agency to address this issue.

Cardiovascular effects: No data were submitted; this is a 505(b)(2) application that relies upon a prior finding of the Agency to address this issue.

Pulmonary effects: No data were submitted; this is a 505(b)(2) application that relies upon a prior finding of the Agency to address this issue.

Renal effects: No data were submitted; this is a 505(b)(2) application that relies upon a prior finding of the Agency to address this issue.

Gastrointestinal effects: No data were submitted; this is a 505(b)(2) application that relies upon a prior finding of the Agency to address this issue.

Abuse liability: No data were submitted; this is a 505(b)(2) application that relies upon a prior finding of the Agency to address this issue.

Other: No data were submitted; this is a 505(b)(2) application that relies upon a prior finding of the Agency to address this issue.

2.6.2.5 Pharmacodynamic drug interactions

No data were submitted; this is a 505(b)(2) application that relies upon a prior finding of the Agency to address this issue.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

No data were submitted; this is a 505(b)(2) application that relies upon a prior finding of the Agency to address this issue.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Quoting the submission:

> "Metronidazole is rapidly and nearly totally absorbed after oral administration; the pharmacokinetic profile, as seen in the rat, is similar to that observed in humans. The drug is not significantly bound to serum proteins and distributes well to all body compartments with the lowest concentration found in fat. Metronidazole produces minimal, if any, enzyme induction or inhibition. The metabolism is similar with species-related differences in qualitative and quantitative amounts of oxidized and conjugated metabolites. Metronidazole is excreted primarily in the urine as parent drug, oxidative metabolites, and conjugates."

Please see the Clinical Pharmacology and Biopharmaceutics review for further information.

2.6.4.2 Methods of Analysis

Not applicable.

2.6.4.3 Absorption

No data were submitted; this is a 505(b)(2) application.

2.6.4.4 Distribution

No data were submitted; this is a 505(b)(2) application.

2.6.4.5 Metabolism

No data were submitted; this is a 505(b)(2) application.

2.6.4.6 Excretion

No data were submitted; this is a 505(b)(2) application.

2.6.4.7 Pharmacokinetic drug interactions

No data were submitted; this is a 505(b)(2) application.

2.6.4.8 Other Pharmacokinetic Studies

No data were submitted; this is a 505(b)(2) application.

2.6.4.9 Discussion and Conclusions

Definitive nonclinical pharmacokinetic data were not submitted, as this is a 505(b)(2) application. Please see the Clinical Pharmacology and Biopharmaceutics review for further information.

2.6.4.10 Tables and figures to include comparative TK summary

No data are available; this is a 505(b)(2) application.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: No toxicity was observed in a series of repeat-dose topical toxicology studies, including a 4-week study conducted with rats and 13-week studies involving rabbits and minipigs.

Genetic toxicology: No new data were submitted. According to the label of the RLD (Noritate Cream), "metronidazole has shown evidence of mutagenic activity in several *in vitro* bacterial assay systems. In addition, a dose-related increase in the frequency of micronuclei was observed in mice after intraperitoneal injections. An increase in chromosomal aberrations in peripheral blood lymphocytes was reported in patients with Crohn's disease who were treated with 200 to 1200 mg/day of metronidazole for 1 to 24 months. However, in another study, no increase in chromosomal aberrations in circulating lymphocytes was observed in patients with Crohn's disease treated with the drug for 8 months".

Carcinogenicity: No new data were submitted. According to the label of the RLD (Noritate Cream), "metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters. In several long term studies in mice, oral doses of approximately 225 mg/m ^{2} /day or greater (approximately 37 times the human topical dose on a mg/m ^{2} basis) were associated with an increase in pulmonary tumors and lymphomas. Several long term oral studies in the rat have shown statistically significant increases in mammary and hepatic tumors at doses >885 mg/m ^{2} /day (144 times the topical human dose). In one published study, using albino hairless mice, intraperitoneal administration of metronidazole at a dose of 45 mg/m ^{2} /day (approximately 7 times the human topical dose on a mg/m ^{2} basis) was associated with an increase in ultraviolet radiation-induced skin carcinogenesis. Neither dermal carcinogenicity nor photocarcinogenicity studies have been performed with [the product] or any marketed metronidazole formulations".

Reproductive toxicology: Metronidazole did not induce teratogenic events in mice or rats. Metronidazole has not been evaluated as a developmental toxicant in nonrodents or for effects upon fertility or perinatal development.

Special toxicology: The drug product was essentially nonirritating to either skin or eyes, and did not induce sensitization.

2.6.6.2 Single-dose toxicity

No data were submitted; this is a 505(b)(2) application that relies upon a prior finding of the Agency to address this issue.

2.6.6.3 Repeat-dose toxicity

1. Study title: Sub-chronic (4 weeks) toxicity study by the cutaneous route in the Sprague-Dawley strain of rat of Rozex lotion and Rozex gel containing metronidazole at 0.75% (w/w).

Key study findings: No toxicity was observed in this study. Note: The formulations tested in this study contained a lower concentration of metronidazole than does the subject of NDA 21-789.

Study No.: 1.CG.03.SPR.8163. [redacted]
Document #, Volume #, and Page #: NA
Conducting laboratory and location: [redacted]
Date of study initiation: 12-SEP-1994
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Rozex lotion formulation (exact formulation not stated, but it contained metronidazole 0.75% w/w, lot No. 562.203/2F2. Rozex gel formulation (contained metronidazole 0.75% w/w), Lot No. not specified. Note: Rozex products are presumably marketed in Europe.

Formulation/vehicle: Not stated, but the test articles contained 0.75% w/w metronidazole.

Methods (unique aspects):

Dosing:

Species/strain: Rat/ [redacted] Sprague-Dawley
#/sex/group or time point (main study): 5/sex/group
Satellite groups used for toxicokinetics or recovery: Yes (5/sex/group for TK in treatment groups and 2/sex in control group)
Age: Not stated that I could find
Weight: At start of dosing: Males approx. 180 g; females approx. 175 g

Doses in administered units: Controls were not treated. Test animals received either Rozex 0.75% lotion or gel in a volume of 2 mL/kg/day, applied to a shaved area that equaled approximately 10% of the body surface area. Note: Expression of topically-applied dosages in terms of unit-volume per unit of body weight (mL/kg) is rather meaningless, but I will use these units for want of better terms. It is unclear how much test material was removed and discarded when the treated area was washed following the six hour exposure period each day.

Route, form, volume, and infusion rate: Topical, 2 mL/kg/day once per day for at least 28 consecutive days. The assigned material was applied to shaved skin and gently rubbed into the treatment site for 30 seconds. The treated area was apparently not covered. The treatment site was washed with water and blotted dry six hours following application on Tuesdays through Saturdays, and immediately prior to the next application on Sundays and Mondays. The animals wore Elizabethan collars during the exposure period to minimize ingestion.

Observations and times:

Clinical signs: Animals observed daily
Examination of treatment site (erythema/edema): Daily
Body weights: Weekly
Food consumption: Approx. weekly
Ophthalmology: No
EKG: No
Hematology: Yes, during week 4
Clinical chemistry: Yes, during week 4
Urinalysis: No
Gross pathology: All animals
Organs weighed: Adrenals, brain, heart, kidneys, liver, ovaries, thyroid, spleen, testes
Histopathology: Yes, limited to bone (femur), esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, heart, kidneys, liver, treated skin, and untreated skin from all groups
Toxicokinetics: Blood samples obtained on first day of dosing and on day 28 at 4 hours post-treatment

Results:

- Mortality: No unscheduled deaths
- Clinical signs: No remarkable observations, including skin at treatment site
- Body weights: No remarkable observations
- Food consumption: No remarkable observations
- Ophthalmology: NA
- EKG: NA
- Hematology: No remarkable observations
- Clinical chemistry: No remarkable observations
- Urinalysis: NA
- Organ Weights: No remarkable observations.

- Gross pathology: No remarkable observations
- Histopathology: No remarkable observations
- Toxicokinetics:

Plasma Concentration of Metronidazole, 4 Hours Post-Application (ng/mL):

Days of Dosing	Males	Females
1	207	170
28	736	922

2. Study title: 13-week dermal toxicity study in rabbits.

Key study findings: No toxicity was observed in this study. Note: The formulation tested in this study contained a lower concentration of metronidazole than does the subject of NDA 21-789.

Study No.: 6205-100
Document #, Volume #, and Page #: NA
Conducting laboratory and location: [redacted]
Date of study initiation: 28-APR-1986
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Metronidazole gel 0.75%, lot No. [redacted] 6-09105. Placebo gel, Lot No. [redacted] -7-03106.

Formulation/vehicle: The specific formulation tested was not specified, other than that it contained 0.75% metronidazole and was manufactured by [redacted]

Methods (unique aspects):

Dosing:
Species/strain: Rabbits/Hra:(NZW)SPF
#/sex/group or time point (main study): 5/sex/group; housed 1 per cage
Satellite groups used for toxicokinetics or recovery: No
Age: Not stated that I could find
Weight: At start of dosing: Approx. 2.5 kg
Doses in administered units: Controls received 1.77 mL/kg/day of placebo (vehicle) gel. Test animals received either 0.017 (low-dose group), 0.18 (mid-dose group), or 1.77 (high-dose group) mL/kg/day of 0.75% metronidazole gel, applied to 10% of the body surface. Note: Expression of topically-applied dosages in terms of unit-volume per unit of body weight (mL/kg) is rather meaningless, but I will use these units for want of better terms. It is unclear

how much test material was removed and discarded when the dressing was removed and the site washed each day.

Route, form, volume, and infusion rate: Topical, 0.017, 0.18, or 1.77 mL/kg/day (see above) once per day for at least 13 consecutive weeks. The assigned material was applied to shaved skin. The treated area was not covered with a dressing, but the animals were collared to prevent ingestion of the test material. The application site was wiped with wet paper towels prior to each application to remove remaining material.

Observations and times:

Clinical signs: Animals observed twice daily
Examination of treatment site (erythema/edema): Daily
Body weights: Weekly
Food consumption: Weekly
Ophthalmology: No
EKG: No
Hematology: Yes, at termination
Clinical chemistry: Yes, at termination
Urinalysis: No
Gross pathology: All animals
Organs weighed: Brain, kidneys, liver, testes
Histopathology: Yes, full list from control and high-dose animals
Toxicokinetics: No

Results:

- Mortality: One control male was found dead during week 2; this was considered incidental. No other unscheduled deaths
- Clinical signs: No remarkable observations, including skin at treatment site
- Body weights: No remarkable observations
- Food consumption: No remarkable observations
- Ophthalmology: NA
- EKG: NA
- Hematology: No remarkable observations
- Clinical chemistry: No remarkable observations
- Urinalysis: NA
- Organ Weights: No remarkable observations.
- Gross pathology: No remarkable observations
- Histopathology: No remarkable observations
- Toxicokinetics: NA

3. Study title: A 3-month dermal toxicity study of metronidazole gel (1%) in Hanford minipigs.

Key study findings: No toxicity was observed in this study.

Study No.: 3551.7
Document #, Volume #, and Page #: NA
Conducting laboratory and location: [redacted]
Date of study initiation: 05-JUN-2001
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Metronidazole gel 1%, lot No. GLP-015. Placebo gel, Lot No. GLP-014. Note: The specific formulation tested was not specified.

Formulation/vehicle: See second page of this review.

Methods (unique aspects):

Dosing:

Species/strain: Hanford minipigs
#/sex/group or time point (main study): 4/sex/group; housed 1 per pen
Satellite groups used for toxicokinetics or recovery: No
Age: Not stated that I could find
Weight: At start of dosing: Approx. 14 kg
Doses in administered units: Controls received 0.10 mL/kg/day of placebo (vehicle) gel, applied to 100 cm^2 of skin. Test animals received either 0.01 (low-dose group), 0.03 (mid-dose group), or 0.10 (high-dose group) mL/kg/day of 1% metronidazole gel, applied to 10 cm^2, 35 cm^2, or 100 cm^2, respectively. Note: Expression of topically-applied dosages in terms of unit-volume per unit of body weight (mL/kg) is rather meaningless, but I will use these units for want of better terms. It is unclear how much test material was removed and discarded when the dressing was removed and the site washed each day.
Route, form, volume, and infusion rate: Topical, 0.01, 0.03, or 0.1 mL/kg/day (see above) once per day for at least 91 consecutive days. The assigned material was applied to shaved skin and gently rubbed into the treatment site with a glass rod. The treated area was covered with an 8-ply gauze dressing, which was secured with tape and covered with a stockinette sleeve. It is unclear to what extent the dressing occluded the treatment site. The treatment site was wiped clean of residual material prior to each treatment with saline-soaked gauze.

Observations and times:

Clinical signs: Animals observed twice daily (detailed clinical exam weekly)
Examination of treatment site (erythema/edema): Twice weekly
Body weights: Weekly
Food consumption: No
Ophthalmology: Yes, on days -13 and 86
EKG: Yes, on days -3, 42, and 89
Hematology: Yes, before start of treatment and weeks 7 and 13
Clinical chemistry: Yes, before start of treatment and weeks 7 and 13
Urinalysis: No

Gross pathology: All animals
Organs weighed: Adrenals, brain, heart, kidneys, liver, ovaries, thyroid, pituitary, spleen, testes
Histopathology: No
Toxicokinetics: Blood samples drawn from males on day 84 and females on day 88 at 0.5, 1, 2, 4, 8, and 24 hours post-application for toxicokinetic analysis.

Results:

- Mortality: No unscheduled deaths
- Clinical signs: No remarkable observations, including skin at treatment site
- Body weights: No remarkable observations
- Food consumption: NA
- Ophthalmology: No remarkable observations
- EKG: No remarkable observations
- Hematology: No remarkable observations
- Clinical chemistry: No remarkable observations
- Urinalysis: NA
- Organ Weights: No remarkable observations.
- Gross pathology: No remarkable observations
- Histopathology: NA (not performed)
- Toxicokinetics: Samples were analyzed for concentration of metronidazole (LOQ [redacted] ng/mL) and 2-hydroxymethyl-metronidazole (a metabolite; LOQ [redacted] ng/mL). Virtually all the samples were [redacted] the limit of quantitation (LOQ) for both compounds, although several of the male animals were slightly [redacted] the LOQ for metronidazole between 0.5 and 4 hours post-dosing.

2.6.6.4 Genetic toxicology

According to the label of the RLD (Noritate Cream), "metronidazole has shown evidence of mutagenic activity in several *in vitro* bacterial assay systems. In addition, a dose-related increase in the frequency of micronuclei was observed in mice after intraperitoneal injections. An increase in chromosomal aberrations in peripheral blood lymphocytes was reported in patients with Crohn's disease who were treated with 200 to 1200 mg/day of metronidazole for 1 to 24 months. However, in another study, no increase in chromosomal aberrations in circulating lymphocytes was observed in patients with Crohn's disease treated with the drug for 8 months".

Genetic toxicology summary: Metronidazole is mutagenic and clastogenic.

Genetic toxicology conclusions: Metronidazole is a genetic toxicant.

Labeling recommendations: See below.

2.6.6.5 Carcinogenicity

According to the label of the RLD (Noritate Cream), "metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters. In several long term studies in mice, oral doses of approximately 225 mg/m ^{2}/day or greater (approximately 37 times the human topical dose on a mg/m ^{2} basis) were associated with an increase in pulmonary tumors and lymphomas. Several long term oral studies in the rat have shown statistically significant increases in mammary and hepatic tumors at doses >885 mg/m ^{2}/day (144 times the topical human dose). In one published study, using albino hairless mice, intraperitoneal administration of metronidazole at a dose of 45 mg/m ^{2}/day (approximately 7 times the human topical dose on a mg/m ^{2} basis) was associated with an increase in ultraviolet radiation-induced skin carcinogenesis. Neither dermal carcinogenicity nor photocarcinogenicity studies have been performed with [the product] or any marketed metronidazole formulations".

Carcinogenicity summary: Metronidazole is a rodent carcinogen, causing pulmonary tumors and lymphomas in mice and mammary and hepatic tumors in rats. It may also be a photococarcinogen.

Carcinogenicity conclusions: Metronidazole is carcinogenic.

Labeling Recommendations: See below.

2.6.6.6 Reproductive and developmental toxicology

Quoting the label of the RLD (Noritate Cream), "Pregnancy Category B. There are no adequate and well controlled studies with the use of [the product] in pregnant women. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral administration of metronidazole to rats or mice at 200 and 20 times, respectively, the expected clinical dose. However, oral metronidazole has shown carcinogenic activity in rodents. Because animal reproduction studies are not always predictive of human response, [the product] should be used during pregnancy only if clearly needed".

Reproductive and developmental toxicology summary: Metronidazole has been evaluated for teratogenic potential in mice and rats, and negative results were obtained. Metronidazole has apparently not been evaluated for teratogenic potential in a nonrodent species. Metronidazole has apparently not been evaluated for effects upon fertility or perinatal development.

Reproductive and developmental toxicology conclusions: Metronidazole did not induce teratogenic events in mice or rats. Metronidazole has not been evaluated as a developmental toxicant in nonrodents or for effects upon fertility or perinatal development.

Labeling recommendations: See below.

2.6.6.7 Local tolerance

1. Study title: A primary skin irritation study in rabbits with metronidazole gel 1%

Key study findings: The test materials do not appear to be excessively irritating.

Study no: 0215-R2.R-01-01
Volume #, and page #: NA
Conducting laboratory and location: [redacted]
Date of study initiation: 13-JUN-2001 (date protocol signed)
GLP compliance: Yes
QA reports: yes (X) no ( ):
Drug, lot #, radiolabel, and % purity: Metronidazole 1% gel, Batch No. GLP-015
Formulation/vehicle: A formulation was tested that was similar to the current clinical formulation, except that it contained 4%-5% [redacted] instead of 1% [redacted]. Vehicle was used as the control.

Methods:
Dosing: Male New Zealand rabbits were used. Metronidazole 1% gel was applied to two shaved sites on the dorsal surface on six animals; one site on each animal was abraded. Vehicle was applied to 3 animals. Application consisted of placement of 0.5mL of test material on the selected sites followed by coverage of the areas with an occlusive dressing (gauze wrapped with plastic). Elizabethan collars were placed on the animals. The dressings and any remaining material were removed 24 hours after placement.

Observations and times: The treatment sites were examined for erythema and edema 1, 24, 48, and 72 hours after removal of the dressing. The animals were observed daily until resolution of any reactions.

Results: The test materials induced very slight to slight erythema and edema that cleared within 10 days. The vehicle and active gels produced similar reactions. These reactions may have been at least partially due to the shaving and bandaging procedures that were used. A sham-operated control (animals shaved and bandaged with no gel application) was not included in the study.

Summary of individual study findings: Metronidazole 1% gel, as tested, produced very slight to slight erythema and edema under the conditions of this study.

Conclusions: The test materials do not appear to be excessively irritating.

2. Study title: FHSA primary dermal irritation

Key study findings: The test material apparently was not excessively irritating.

Study no: 0215-R2.R-03-02
Volume #, and page #: NA
Conducting laboratory and location: [redacted]

Date of study initiation: 30-JAN-2002 (date protocol signed)
GLP compliance: Yes
QA reports: yes (X) no ( ):
Drug, lot #, radiolabel, and % purity: Metronidazole 1% gel, Batch No. GLP-015
Formulation/vehicle: A formulation similar to the current drug product, which contained 0.5%-1.5% [redacted] was used. Apparently no control material was used.

Methods:
Dosing: Female rabbits were used; the strain was not identified. Metronidazole 1% gel was applied to two shaved sites on the dorsal surface on six animals; one site on each animal was abraded. Application consisted of placement of 0.5 mL of test material on gauze pads which were taped over the selected sites followed by coverage of the areas with an occlusive dressing. The dressings and any remaining material were removed 24 hours after placement.

Observations and times: The treatment sites were examined for erythema and edema 24 and 72 hours after application of the test material.

Results: Slight erythema (score of 1 on a scale of 4) was observed in four of six animals at the 24 hour observation time. Apparently no other reactions were observed.

Summary of individual study findings: Metronidazole 1% gel, as tested, apparently produced slight erythema that cleared within 48 hours. No other reactions were reported.

Conclusions: The test material apparently was not excessively irritating.

3. Study title: Primary skin irritation potential of a metronidazole gel 1%. Note: Conducted to meet OSHA requirements under 16 CFR 1500.41.

Key study findings: The test material was not irritating under the conditions of this study.

Study no: X2G372G; also, study No. 0215-R2.R-04-02
Volume #, and page #: NA
Conducting laboratory and location: [redacted]

Date of study initiation: 13-AUG-2002 (date protocol signed)
GLP compliance: Yes
QA reports: yes (X) no ( ):
Drug, lot #, radiolabel, and % purity: Metronidazole 1% gel, Batch No. 755

Formulation/vehicle: Metronidazole 1% gel, specific formulation not indicated.

Methods:
Dosing: Male New Zealand rabbits were used. Metronidazole 1% gel was applied to two shaved sites on the dorsal surface on six animals; one site on each animal was abraded. Application consisted of placement of 0.5 mL of test material on the selected sites followed by coverage of the areas with gauze that was held in place with tape and wrapped with an elastic bandage. The dressings and any remaining material were removed 24 hours after placement.

Observations and times: The treatment sites were examined for erythema and edema 24 and 72 hours after removal of the dressing.

Results: No signs of irritation, including edema and erythema, were observed.

Summary of individual study findings: Metronidazole 1% gel, as tested, produced no erythema or edema under the conditions of this study.

Conclusions: The test material was not irritating.

4. Study title: Primary eye irritation potential of metronidazole gel 1%. Note: Conducted to meet OSHA requirements under 16 CFR 1500.41.

Key study findings: The test material was not irritating to the eyes under the conditions of this study.

Study no: X2G373G; also, study No. 0215-R2.R-05-02
Volume #, and page #: NA
Conducting laboratory and location: [redacted]

Date of study initiation: 13-AUG-2002 (date protocol signed)
GLP compliance: Yes
QA reports: yes (X) no ( ):
Drug, lot #, radiolabel, and % purity: Metronidazole 1% gel, Batch No. 755
Formulation/vehicle: Metronidazole 1% gel, specific formulation not indicated.

Methods:
Dosing: Male New Zealand rabbits were used. 0.1 mL of metronidazole 1% gel was applied undiluted into the right eye of each of six animals and the lids were held closed for 1 second. The left eyes served as controls. All eyes were rinsed with saline 24 hours post-application.

Observations and times: The eyes were examined grossly for corneal ulceration or opacity, inflammation of the iris, and redness and chemosis of the conjunctiva 24, 48, and 72 hours after instillation of the test material.

Results: No signs of irritation were observed.

Summary of individual study findings: Metronidazole 1% gel, as tested, produced no ocular irritation under the conditions of this study.

Conclusions: The test material was not irritating to the eyes.

2.6.6.8 Special toxicology studies

1. Study title: A dermal sensitization study in guinea pigs with metronidazole gel, 1%, maximization design

Key study findings: The test materials were not sensitizing under the conditions of this study.

Study no: 0215-R2.R-02-01
Volume #, and page #: NA
Conducting laboratory and location: [redacted]
Date of study initiation: 13-JUN-2001 (date protocol signed)
GLP compliance: Yes
QA reports: yes (X) no ( ):
Drug, lot #, radiolabel, and % purity: Metronidazole 1% gel, Batch No. GLP-015
Formulation/vehicle: A formulation was tested that was similar to the current clinical formulation, except that it contained 4%-5% [redacted] instead of 1% [redacted]. Vehicle was used as the control.

Methods:
Dosing: Hartley guinea pigs were used. Metronidazole 1% gel was diluted in deionized water (5% w/v) and, on day 0, injected (with or without Freund's complete adjuvant) intradermally into each animal according to standard procedures. Control animals received similar injections without metronidazole gel. On day 6, the injection sites were reshaved and 10% sodium lauryl sulfate in petrolatum was spread over the areas. On day 7, the SLS-petrolatum was removed and gauze containing either metronidazole gel (test) or water (control) was placed over the injection sites and held in place with a bandage. The gauze pads were removed 48 hours later. Metronidazole 1% gel (the drug product) was applied to all sites (both test and control) on day 20 and held in place for 24 hours.

Observations and times: The test sites were examined for erythema and edema at 24 and 48 hours following removal of the gel.

Results: No erythema or edema was observed in any animal at any time point. The conducting laboratory has historical control data on file, obtained in similar studies in which hexylcinnamaldehyde was used as a positive control material, which validate the test methodology.

Summary of individual study findings: Metronidazole 1% gel, as tested, was not a sensitizer.

Conclusions: The test material is apparently non-sensitizing.

2. Study title: Dermal sensitization of metronidazole gel 1% in guinea pigs - Magnusson-Kligman (ISO) method.

Key study findings: The test material was not sensitizing under the conditions of this study.

Study no: X2G374G; also, study No. 0215-R2.R-06-02
Volume #, and page #: NA
Conducting laboratory and location: [redacted]

Date of study initiation: 20-AUG-2002
GLP compliance: Yes
QA reports: yes (X) no ( ):
Drug, lot #, radiolabel, and % purity: Metronidazole 1% gel, Batch No. 755
Formulation/vehicle: Metronidazole 1% gel, specific formulation not specified.

Methods:
Dosing: Hartley guinea pigs were used. Metronidazole 1% gel was diluted in water for injection (25% v/v) and, on day 0, injected (with or without Freund's complete adjuvant) intradermally into each animal according to standard procedures. Control animals received similar injections without metronidazole gel (negative controls) or with DNCB (positive controls). On day 7, either undiluted metronidazole gel, water, or DNCB was administered topically to the injection sites and held in place for 48 hours. On day 21 the animals were challenged with either metronidazole 1% gel or DNCB, applied topically for 24 hours.

Observations and times: The test sites were examined for erythema and edema at 24, 48, and 72 hours following removal of the materials.

Results: Essentially no erythema or edema was observed in any animal at any time point following treatment with metronidazole gel. Appropriate reactions were observed with DNCB.

Summary of individual study findings: Metronidazole 1% gel, as tested, was not a sensitizer.

Conclusions: The test material is apparently non-sensitizing.

2.6.6.9 Discussion and Conclusions

This is a 505(b)(2) application for a topical metronidazole 1% gel product. The primary basis for approval of the product from a nonclinical perspective is the prior finding of the Agency that a similar product, (Noritate (1% metronidazole) cream, NDA 20-743, Galderma, approved 26-SEP-1997), was safe and effective. Additional evidence of safety was provided by a series of studies conducted with the subject of NDA 21-789 (the current clinical formulation or a very closely related formulation). These studies included a 13-week repeat-dose topical dermal toxicology study conducted with minipigs, as well as assays for potential to induce skin or eye irritation or sensitization. No remarkable toxicity was observed in those studies. The excipients and impurities in the product have been qualified. The only noteworthy excipients in the product are betadex, [redacted] and niacinamide, USP, which are present in the product at concentrations of 1% and 1.25%, respectively. Betadex was evaluated in 52-week repeat-dose (dietary) toxicology studies in rats and dogs[1]. No-adverse-effect-levels (NOAELs) of approximately 750 mg/kg/day in rats and approximately 1850 mg/kg/day in dogs were reported. These levels far exceed any human exposure to Betadex that might result from use of the drug product. The exposure to niacinamide would be approximately 25 mg per day or less, applied to the skin. To place this exposure in perspective, niacinamide is used interchangeably with niacin as a dietary supplement (for treatment and prevention of niacin deficiency). The US RDA (recommended dietary allowance) for niacin (or niacinamide) for adults is 14-16 mg by mouth per day. Therefore, the maximum daily exposure to niacinamide, applied to skin, is similar to the US RDA for this material by mouth. Additional evidence of safety of the proposed exposure to niacinamide is provided by the fact that no remarkable toxicity was observed in topical nonclinical and clinical studies conducted with formulations that contained niacinamide.

2.6.6.10 Tables and Figures

Not applicable.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The product is approvable with respect to nonclinical concerns under a 505(b)(2) application.

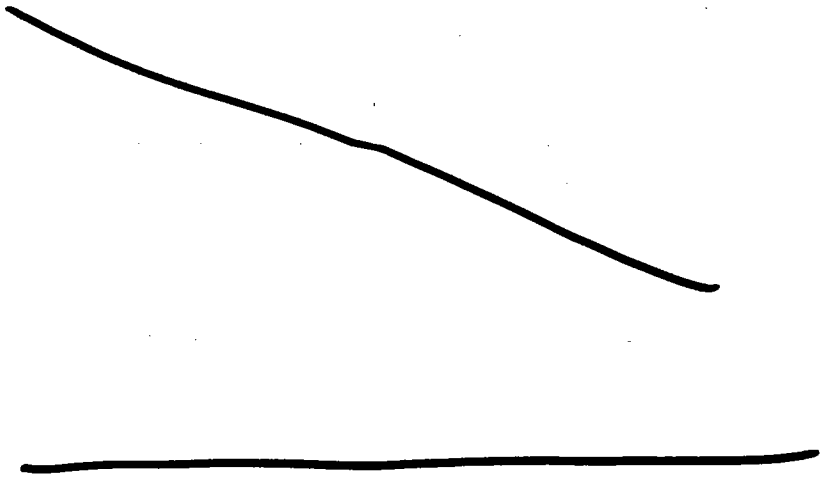
Unresolved toxicology issues (if any): None

[1] B-Cyclodextrin: 52-Week Toxicity Studies in the Rat and Dog. Bellringer, M.E., et al. Fd Chem. Toxic. Vol. 33, No. 5, pp. 367-376, 1995.

Recommendations: The product is approvable with respect to nonclinical concerns under a 505(b)(2) application. Changes to be made in the proposed labeling of the product are indicated below.

Suggested labeling:

The draft label contains a section that reads:



This [redacted] section should be deleted, since it is not Agency policy to describe such nonclinical data in labeling.

The remainder of the label, including the "Pregnancy", "Carcinogenesis, Mutagenesis and Impairment of Fertility", and "Nursing Mothers" sections were lifted verbatim from the label of the RLD product's label (Noritate Cream), and are acceptable with respect to nonclinical issues.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

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

/s/

Norman See
3/4/05 01:51:41 PM
PHARMACOLOGIST

Paul Brown
3/4/05 05:08:28 PM
PHARMACOLOGIST