CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-743

PHARMACOLOGY REVIEW(S)

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

NDA 20-743.bc (Amendment, dated 7/1/97)

Drug Name: Noritate^{R} (metronidazole) Cream, 1%

JUL 11 1997

Category: Antibacterial, antiparasitic

Indication: Treatment of rosacea

Sponsor: Dermik Laboratories, Inc., Collegeville, PA

Number of Vols.: One

Date CDER Received: 7/3/97

Date Assigned: 7/10/97

Date Review Started: 7/11/97

Date 1st Draft Completed: 7/11/97

Date Review Accepted by Supervisor:

Review Objective: To determine adequacy of the labeling

Preclinical Studies: None submitted in this amendment.

Evaluation and Comments: During the labeling day meeting held on 7/9/97, the review team made some significant changes to the proposed draft labeling of the Sponsor. These changes in the pharmacology/toxicology areas have already been incorporated in the most recent labeling proposed by the FDA. This is presented as Attachment 1.

Recommendation to the PM: Please incorporate in the FDA draft labeling the pharmacology/toxicology sections from Attachment 1.

Syed N. Alam, Ph.D.
Pharmacologist

HFD-540/DD/Concur/Wilkin 7/12/97

HFD-540/TL/Concur/Jacobs 7/11/97

cc:
NDA 20-743

HFD-540/

HFD-540/Pharm/Alam

HFD-540/TLPharm/Jacobs

HFD-540/MO/Ko

HFD-540/Chem/Higgins

HFD-540/CSO/Cintron

ATTACHMENT 1

5 Pages (3-7)
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Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products (HFD-540)

NDA 20-743BL (Amendment, dated 4/14/97)

Drug Name: Noritate^{R} (metronidazole 1% cream)

APR 2 8 1997

Category: Antiprotozoal/antibacterial agent

Indication: Treatment of rosacea

Sponsor: Dermik Laboratories, Collegeville, PA

Number of Vols.: One

Date CDER Received: 4/15/97

Date Assigned: 4/23/97

Date Review Started: 4/25/97

Date 1st Draft Completed: 4/28/97

Date Review Accepted by Supervisor:

Related Submissions: DMF , NDA 20-531 (0.75% cream)

Comments:

This is the Sponsor's response to FDA fax dated February 26, 1997 enumerating the recommended pharmacology changes in the draft labeling. These are addressed in the same order as the Sponsor's response.

Recommendation to the Project Manager:

Comments 1 - 4 made above should be communicated to the Sponsor. If the Sponsor wishes, a teleconference may be arranged to discuss any of these points.

Syed N. Alam, Ph.D.
Pharmacologist

HFD-540/DD/Concur/Wilkin 5/16/97

HFD-540/TL/Concur/Jacobs 4/24/97

cc:
NDA 20-743

HFD-340/

HFD-540/

HFD-540/Pharm/Alam

HFD-540/TL/Jacobs

HFD-540/MO/Ko

HFD-540/Chem/via DeCamp (Higgins)

HFD-540/CSO/Cintron

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

NDA 20-743.000 (Original Submission, dated 9/30/96)

Drug Name: Noritate^{R} (metronidazole 1% cream, topical) FEB 7 1997

Category: Antiprotozoal/antibacterial agent

Indication: Treatment of rosacea including inflammatory papules, pustules and erythema

Sponsor: Dermik Laboratories, Collegeville, PA

Number of Vols.: 25

Date CDER Received: 10/2/96

Date Assigned: 10/9/96

Date Review Started: 1/21/96

Date 1st Draft Completed: 2/5/97

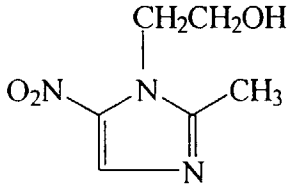
Date Review Accepted by Supervisor:

Related Submissions: IND '; NDAs 19-737 (0.75% gel), 20-208 (0.75% vaginal gel), 20-531 (0.75% cream), 20-334 (Flagyl oral capsules)

Review Objective: To determine approvability of the application from pharmacology standpoint.

Chemical Name: 2-Methyl-5-nitroimidazole-1-ethanol

Structure:



Composition:

Ingredient	Mg/Gm
Metronidazole, USP, micronized	
Stearic Acid, NF	
Glyceryl Monostearate, NF (myverol 18-07)	
Glycerin, USP	
Methylparaben, NF	
Propylparaben, NF	
Triethanolamine, NF	
Purified Water, USP	

Index of Studies:

The following reports are new to this NDA, and have never been published or submitted to any Regulatory Agency. The present formulation was not the subject of these studies.

1. Rabbit eye irritation study with metronidazole 0.1% cream formulations. Report 86342D/ICP 9/SE

2. Phototoxicity and photoallergic potentials of topical metronidazole cream 1% in guinea pigs. Report 701340-

3. One month dermal toxicity study of Flagyl (metronidazole) solution (0.5% w/v) in rats. Reports R Tox 212 and R.Ph.331 (Pharmacokinetics).

4. 28-Day dermal toxicity study in rabbits with Flagyl (metronidazole) solution (0.5% w/v). Reports R Tox. 222 & R.Ph. 332

5. Bacterial mutagenicity test with Salmonella and E. coli strains with secnidazole and metronidazole. Report C.R. Vitry/C.N.G. No. 21 555 BOA/PA.

6. Studies on possible cause of metronidazole (RP 8823) mutagenic activity. Report ST/C.R.V./Tox. No. 130.

7. In vitro DNA repair test on primary rat hepatocyte culture with metronidazole. Report ST/C.R.V. /Tox. No. 132.

8. Metronidazole (8823 R.P.): CHO/HGPRT test. Report ST/C.R.V./Tox. No. 143.

9. Chromosomal aberration test on Chinese hamster ovary cells. Report ST/C.R.V./Tox. No. 167.

10. 2-Year oral carcinogenicity study in mice with metronidazole and secnidazole . RP Study No. 347-004.

11. 2-Year oral carcinogenicity study in rat with metronidazole and secnidazole. RP Study No. 347-005.

12. Summaries of previously published or submitted studies which have been reviewed by various Reviewers over the years in connection with NDAs and/or INDs for other formulations of metronidazole.

Review of Preclinical Studies (new to this NDA). No studies have been performed with the proposed clinical cream formulation.

1. Rabbit eye irritation study with metronidazole cream formulations

A 0.1 ml aliquot of each of 0.5%, 1% and 2% metronidazole cream formulations was placed in the lower lid of one eye of each of three New Zealand White rabbits. The contralateral eyes were the controls. The eyes were examined after 1 hour and 1, 2, 3, 4 and 7 days. Mild conjunctival irritation was noted in 2 of 3 rabbits in all groups. No rabbits showed corneal or iridial inflammation. The incidence and severity of eye irritation were similar in the drug and placebo-treated groups. Within 1 to 3 days of instillation all eyes were normal.

2. Phototoxicity and photoallergic potentials of metronidazole cream 1% .

The cutaneous phototoxic and photoallergic potential of a metronidazole 1% cream was evaluated in 20 Dunkin-Hartley albino guinea pigs. The control group (group 1), had 3 males and 2 females, and the test group (group 2) had 10 males and 10 females. To determine phototoxicity, a single occlusive application of 0.25 ml of test material was made on a clipped and depilated area on the guinea pig back and left for 90 minutes followed by irradiation (UVA and UVB, M.E.D.). The extent of irritation at the site was the measure of phototoxic potential.

Photoallergic potential was determined after 3 additional 90-minute occlusive applications of 0.5 ml of test material followed by irradiation after each application, a 14-day rest period, and then an occluded 90-minute challenge application of 0.25 ml of test material. Animals were observed for signs of local effects at 6, 24 and 48 hours after irradiation.

"From the macroscopic and histological results obtained under the experimental conditions, the test article did not show phototoxic potential. A reaction of photoallergical type was noted in 1 out of the 20 guinea pigs examined (5%), but this result was not considered significant."

3. One month dermal toxicity study in rats, and plasma concentrations of metronidazole in rats.

The effect of a metronidazole 0.5% (w/v) solution on intact and abraded skin of groups of Charles River CD rats was studied after applying dermally for 30 days. The two water control groups together had 24 (12/sex) rats, and each of the intact and abraded skin groups had 12 (6/sex) rats.

An additional 16 (8/sex) rats were used for plasma drug levels determinations. Clinical signs, body weights and hematology values in the control and the test groups were within normal ranges. Abnormally high blood glucose values were reported in 4/6 males and 1/6 females of the

intact skin Flagyl group, and in 1/6 males of the Flagyl treated abraded skin group. Nearly all animals had elevated ALA and SAT levels that were interpreted to be a response to stress.

Dermal collagen thickening was noted in about half of the animals from all the groups except the abraded skin control group where 3/12 animals were affected. Liver necrosis seen in one Flagyl treated abraded skin group was considered incidental.

Plasma metronidazole concentrations

The mean observed plasma metronidazole concentrations were 1.8 μg/ml for male and 4.8 μg/ml for female rats on day 7 of the study, and 3.5 μg/ml for males and 3.7 μg/ml for females on day 30 of the study. Thus, a sex-related difference was observed on day 7 but not on day 30. There was no difference between the intact and abraded skin animals of the same sex.

Duration of dosing (7 days vs. 30 days) had no effect on the metronidazole serum concentrations in the abraded skin animals. In the intact skin groups, however, the serum concentrations in the males increased by 200%, but in the females, it decreased by 37% on day 30 when compared to day 7 values. Thus a sex-related difference was observed during the multiple dosing period.

"The approximate body burden is 1.8% of the dose at 22 hours after dosing.

4. 28-Day dermal toxicity study and plasma concentrations of metronidazole 0.5% solution (w/v) in New Zealand White rabbits.

The effect of an occluded dermal application of metronidazole solution, 0.5% or water (control) on intact and abraded skin of 48 New Zealand White rabbits (12/sex/group) was studied. The materials were applied for 20-22 hours each day for 28 days. Plasma samples obtained at 22 hours after the start of dosing on days 7 and 28 of the study were assayed

for metronidazole and one of its major metabolites, 20396 R.P.M.

No drug treatment-related skin lesions were reported.

The mean (intact and abraded for females) plasma metronidazole concentrations were 0.13 μg/ml for male and 0.15 μg/ml for female rabbits on day 7 of the study and 0.09 μg/ml for male and 0.47 μg/ml for female rabbits on day 28 of the study. For abraded group males, the plasma concentrations could not be calculated because of too few data points. No measurable amount (>0.1 μg/ml) of the metabolite was found. The sex difference in the intact skin group was statistically significant.

Mutagenicity Studies

5. Bacterial mutagenicity test using the mammalian microsome/plate incorporation assay.

After a preliminary cytotoxicity test, the in vitro mutagenicity potential of metronidazole was assessed using Salmonella typhimurium tester strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, and E. coli strain WP 2 uvrA at concentrations of 1000, 500, 250, 125, 62.5 and 31 μg/plate in the plate incorporation assay. Identical tests were performed with and without metabolic activation with rat liver homogenate (S-9 fraction).

Metronidazole showed positive mutagenic activity with TA 1535 and TA 100, and with E. Coli WP2 uvrA strains, both with and without metabolic activation. Thus, in the Ames test, it acts "towards D.N.A. as direct mutagens especially by base-pair substitutions mechanism".

6. Summary of results from investigative studies conducted to ascertain the possible cause (s) of metronidazole's mutagenic activity.

The genotoxic activity of metronidazole, seen in the Ames test, was further investigated

for its mechanism. To this end, two tester strains of Salmonella typhimurium, TA 100 NR^+ (100% nitroreductase activity) and TA 100 NR^- (4% notroreductase activity) were used. Tests were performed both with and without metabolic activation by rat liver homogenate from rats pretreated with Aroclor 1254. Reversion frequencies induced by metronidazole were similar with and without S-9 mix, but reversion frequencies for strain TA 100 NR^+ (with or without S-9 mix) were significantly higher than those of strain TA 100 NR^-.

To test the possibility that mutagenic metabolites may be produced by bacterial flora or mammalian liver, rats were given 200 mg/kg metronidazole either by oral route (effect of bacterial flora and mammalian liver) or by the intravenous route (effect of mammalian liver only), and urine samples were collected and tested for genotoxic activity with the same two bacterial strains. Again, the reversion frequencies induced by urine samples from rats treated by the oral or intravenous routes with metronidazole were similar, but, reversion frequencies for the strain TA 100 NR^+ were clearly higher than those of strain TA 100 NR^-.

Thus, it appears that bacterial nitroreductase in the tester strains was responsible for the production of mutagenic metabolite(s) of metronidazole.

7. Metronidazole (8823 RP): In vitro DNA repair test on primary rat hepatocytes in culture.

Freshly prepared primary hepatocytes were used for a preliminary cytotoxicity test. DNA repair was measured by autoradiographic localization of nuclear radioactivity following treatment with metronidazole and tritiated thymidine. 9-Aminofluorene was the negative control and 2-aminofluorene was the positive control.

Up to a maximal of 2000 µg/ml, no increase in nuclear incorporation of tritiated thymidine was observed. Thus, metronidazole did not exhibit any genotoxicity in this

mammalian in vitro assay system.

8. Metronidazole (8823 RP): CHO/HGPRT test (in vitro mammalian cell test)

Potential mutagenic activity of metronidazole was examined via the increase in the number of mutant HGPRT cells of the Chinese hamster ovary (CHO) K1 cells in vitro. Two separate tests, each with and without metabolic activation (rat liver homogenate), were performed. In the first test, metronidazole was used at 5, 10, 50, 100, 500, 1000, 5000 and 10,000 μg/ml concentrations. There was no clear cytotoxicity at 10,000 μg/ml of metronidazole. There was no increase in the mutant frequency of the cells at any of the above concentrations.
In the second test, 100, 500, 1000, 5000 and 10,000 μg/ml of metronidazole were tested. No mutagenic activity was exhibited by metronidazole at any of the concentrations tested.

9. In vitro clastogenic (chromosomal abnormalities) activity of metronidazole on the Chinese hamster ovary (CHO) cells.

After a preliminary cytotoxicity test, the clastogenic activity of metronidazole was determined in vitro using CHO cells in culture, both in the presence and absence of Aroclor 1254 induced rat liver S-9 fraction. Cyclophosphamide was used as a positive control in the test with metabolic activation, and methyl methanesulfonate was a positive control in the absence of metabolic activation.

Chromosomal aberrations were identified either as visible lesions at the chromosomal level or as a variation in the number of chromosomes.

Metronidazole at concentrations of 1, 250, 2500 and 5000 μg/ml was not a clastogen in this system under the conditions of the experiments.

Carcinogenicity Studies (New)

10. A 2-Year carcinogenicity study of metronidazole in mice.

11. A 2-Year carcinogenicity study of metronidazole in rats.

In both studies (#s 10 and 11), the drug was administered via diet. Both the studies have been reviewed when the original full reports were submitted separately (see Pharmacology Review, NDA 20-743.BP submission, dated 11/13/96). Increased incidences of lung adenomas in mice and hepatic adenoma and carcinoma and mammary gland adenomas in rats were reported.

12. Summary of previous review of toxicology data on metronidazole.

The following is reproduced verbatim from a review of metronidazole toxicity data done by Dr. Avalos in connection with the IND (amendment 14, dated 2/26/96).

"Summary of Toxicity Data:

Note: The following comments represent a summary of all the information collated from four different submissions (IND , IND NDA 19-737, and NDA 20-531). The majority of the data was obtained from the open literature.

The current toxicology for metronidazole is as follows: The long-term oral administration of relative high doses (300 mg/kg/day) of metronidazole decreased the rate of weight gain and altered the male reproductive system in mice and rats. Metronidazole can cause morphological changes in the spermatozoa of mice. In the monkey (150 mg/kg/day), liver morphological abnormalities were observed with no atypical clinical analyses. In addition, high oral doses of metronidazole (75 mg/kg/day) resulted in higher incidences of tumors in mice and rats, but not in hamsters compared to control animals. The doses used in the rat and mice studies approximate 4

and 8 times, respectively, the maximum possible human systemic exposure after a topical administration. This estimate was obtained assuming 100% bioavailability of the oral dose to the animals (a 200 g rat with a surface area of 325 cm^2 and a 20 g mouse with 46 cm^2 surface area) and 100% absorption of the topical human dose (1 g of cream) in a 70 kg individual (surface area = 18000 cm^2).

Metronidazole was mutagenic to certain strains of Salmonella typhimurium, TA 100, TA 98, and E.coli strain WP2uvrA-. Furthermore, a dose-dependent increase in the frequency of micronuclei was observed in mice after intraperitoneal injections of either 23, 70, and 160 mg/kg of metronidazole. In humans with Crohn's disease who were treated with 200-1200 mg/day of metronidazole for 1 to 24 months, a significant increase in the chromosome aberration frequency was reported. However, other genotoxic studies gave negative results. Embryotoxicity and teratogenicity were reported in two rat, one guinea pig, and two mouse studies. Several of the reproductive studies have been previously reviewed by FDA Pharmacologists Harold Carlin and Sandra Morseth (see attached reviews) and were invalidated due to lack of controls (Ivanov, 1969), unreliable results (rabbit studies performed by investigator incompetence (rat studies performed by , and possible mechanical damage during intraperitoneal dosing (Giknis & Damianov, 1983). The remaining studies report negative reproductive findings. The highest doses examined in these studies (200 mg/kg/day in rats and 20 mg/kg/day in mice) represent 29 and 2 times, respectively, the maximum possible human systemic exposure after a topical administration. Because metronidazole is a carcinogen, and is capable of crossing the placental barrier and entering the fetal circulation rapidly, the drug should be used during pregnancy only if clearly needed. The marketed formulations of

metronidazole are designated Pregnancy Category B products.

The phototoxic potential was evaluated in several clinical Phase I trials (NDA 20-531). Both formulations were examined for the ability of metronidazole to elicit a photoirritation or photoallergic reaction in normal human volunteers. Under the conditions of the studies, no evidence for either metronidazole (0.75%) or its vehicles (gel or cream) to elicit such a response was observed during the treatment period (single exposure or 6 exposures over a 3 week period). However, several *in vitro* studies (IND indicate that this compound may become activated or decompose to yield a reactive intermediate with UV irradiation. Metronidazole (100-1000 ug/ml) produced concentration and time dependent photohemolysis of red blood cells with UVA (15 J/cm^2) irradiation after 30 minutes or 24 hours of standing. In addition, metronidazole (10-1000 ug/ml) did produce V79 cellular toxicity, as measured by the decrease in formazan deposition from MTT, with different UVA irradiation doses (1.5-11.25 J/cm^2).

The absorption of metronidazole after a topical administration will result in low systemic plasma concentrations when compared to an oral or intravenous administrations. This low systemic exposure will minimize the potential for a toxic systemic insult. However, the potential for a toxic reaction may exist for metronidazole at the site of application with continuous chronic exposures.

Recent Toxicity Data:

In a recent annual report submission to IND , the effects of long-term drug therapy and UVR irradiation on skin were determined with metronidazole and other compounds. This study was reported in the journal *Photochemistry and Photobiology*, 1989;49(1):59-65. Hairless mice were irradiated daily (290-400 nm), 5 days a week, for the first 12 weeks. The initial UVR

fluence was 0.53 J/cm^2 and this was increased by 20% every 2 weeks to allow for the protective effect of epidermal thickening. After 12 weeks, when the daily UVR fluence dose was 1.60 J/cm^2, the UVR fluence was held at that level while the frequency of UVR was reduced to twice per week. Drug therapy begun 2 weeks following the first UVR treatment and was given on the same days as UVR, but 2 hours prior to UVR. Metronidazole in saline was given (ip) at a dosage of 15 ug/g bw.

Metronidazole had a significant increase in tumor load at 20 and 25 weeks post-UVR. The saline control group has an incidence of 0.37 ± 0.11 and 0.83 ± 0.29 tumors per mouse at 20 and 25 weeks post UVR, respectively. In the metronidazole-treated animals, the tumor per mouse incidence was 3.56 ± 0.45 and 5.63 ± 0.56 at 20 and 25 weeks, respectively. In addition to the increase in tumor incidence, metronidazole also caused an increase in the proportion of keratoacanthomas and carcinomas, and a decrease in papillomas compared to the saline-treated animals."

He further commented that "Since metronidazole absorbs UV light (maximum at 320 nm when dissolved in phosphate buffer or tissue culture media; or maximum at 277 when dissolved in 0.1 M HCl solution), increases the extent of photohemolysis of red blood cells in the presence of UV, decomposes when exposed to UVA light (15 J/cm^2), and enhances the potential dermal photocarcinogenesis, the photobiologic effects of metronidazole need to be addressed by the Sponsor."

Evaluation:

Metronidazole is an antibacterial agent that has been marketed in the USA since 1963 when an oral dosage form was approved for the treatment of trichomoniasis and amoebiasis, and

an intravenous form for serious anaerobic bacterial infections. Since then several topical formulations have been approved. MetroGel[R] 0.75% Topical gel, approved in 1988, is indicated for the treatment of acne rosacea. This was followed by approval in 1992 of MetroGel[R] Vaginal 0.75% for bacterial vaginitis, and MetroCream[R] 0.75% Topical in 1995 for the treatment of inflammatory papules/pustules and erythema of rosacea. A 10% metronidazole vaginal cream has been marketed in Canada since 1970.

The present application is also for a dermal cream formulation for an approved indication (rosacea), but the concentration of metronidazole has been increased to 1%.

No new pharmacology and/or toxicology studies have been performed with the proposed 1% cream formulation. The Sponsor is relying entirely on the existing published and unpublished data base for the safety evaluation of the proposed drug. These reports have been reviewed by Dr. Avalos in connection with the review of IND , and is appended to this review. In a meeting with the FDA, held on April 8, 1996, the Sponsor summarized the available preclinical safety studies (other than the new ones submitted in this application), and sought an agreement from the Agency that no further preclinical safety testing of the product was necessary for the approval of the 1% cream. The reviewing pharmacologist (Dr. Avalos) had agreed with the Sponsor's position, but alerted the Sponsor to address the enhanced photocarcinogenicity of metronidazole reported in the published literature. The study has been reviewed by Dr. Avalos (see his toxicology summary above). It should be noted that metronidazole was administered by intraperitoneal injections, and not by dermal route. The Sponsor has performed a dermal phototoxicity and photoallergenicity study in guinea pigs. The results were negative.

The four new genotoxicity studies submitted in this NDA showed metronidazole to be

mutagenic only in the Ames test with TA 100 and TA 1535 Salmonella strains. It was further shown that metabolite(s) of metronidazole produced by tester strain nitroreductase was probably responsible for the effect. Metronidazole did not affect DNA repair in cultured rat hepatocytes or the HGPRT locus in CHO cells in vitro, and was not clastogenic in CHO cells in vitro, although, in previous in vivo studies, a dose-related increase in the frequency of micronuclei was observed in mice after ip administration of metronidazole.

In the two carcinogenicity studies submitted in this application, increased incidences of lung adenomas in mice and liver and mammary tumors in rats were observed. Similar lesions were reported in several earlier studies and have already been incorporated in one version of the metronidazole labeling (see attached pharmacology review, dated 12/26/96).

No dermal carcinogenicity or photocarcinogenicity study has been performed with any of the metronidazole formulations, including the 10% Canadian cream. All the formulations have, at present, Pregnancy Category B designation. This issue was revisited by Dr. Morseth, formerly of HFD-520 in 1990, who recommended that the present designation (B) be retained, after concluding that the single mouse study showing fetotoxicity, was flawed. Drs. Avalos and Jacobs concurred with that conclusion.

The labeling as submitted in unsatisfactory. It would be necessary to make some changes in the "Carcinogenesis, mutagenesis and impairment of fertility" section as well as in the "Pregnancy" section. The exact changes will be enunciated during labeling review.

Recommendations for the Sponsor:

1. The no-effect dose levels for carcinogenicity in rats and mice should be calculated as mg/m^2 or AUC ratios, if available, and also should be calculated as multiples of projected human dose. A

similar calculation should be made for the teratogenic doses in rodents. These values should be included in the labeling.

3. With the recommended changes in the labeling I find this application approvable.

Syed N. Alam, Ph.D.
Pharmacologist

HFD-540/DD/Concur/Wilkin 2/21/97

HFD-540/TL/Concur/Jacobs 2.21.97

cc:
NDA 20-743

HFD-340/

HFD-540/

HFD-540/Pharm/Alam

HFD-540/TL/Jacobs

HFD-540/MO/Ho

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

NDA 20-743 (New Correspondence, dated 10/28/96)

JAN 4 1997

Drug Name: Noritate[R] (metronidazole 1% cream)

Category: Antibacterial, antiprotozoal and antiinflammatory (?)

Indication: Treatment of Rosacea including inflammatory papules, pustules and erythema

Sponsor: Dermik Laboratories, Inc., Collegeville, PA

Number of Vols.: One

Date CDER Received: 10/30/96

Date Assigned: 11/8/96

Date Review Started: 12/17/96

Date 1st Draft Completed: 12/17/96

Date Review Accepted by Supervisor:

Related Submissions: IND . NDAs: 19-737 (0.75% topical gel), 20-531 (0.75% topical cream); Searle NDA 20-334 (metronidazole capsules); Curatek NDA 20-208 (0.75% vaginal cream)

Comments:

The Sponsor has responded to FDA request for additional information about the 10% metronidazole vaginal cream that has been marketed in Canada since 1970. Labeling as published in the CPS and the Canadian Monograph have been supplied. The issue of animal carcinogenicity bioassay has been mentioned in the labeling very briefly. It reads: "Studies in rats and mice have provided some evidence that metronidazole may cause tumors in these species

when administered orally for a long period at high doses. The relevance of these findings in humans is not known."

The issue has been treated more comprehensively in the "PRODUCT MONOGRAPH". It mentions a mouse study in which at 600 mg/kg dose (diet), there was a statistically significant increase in the rate of benign lung tumors. There was also a trend for increased rate with lower doses. In a 80-week study, rats given 300 mg/kg (diet) dose of metronidazole, there was a significant increase in the number of benign mammary tumors in the females only. Negative hamster studies have also been mentioned. However, the two mouse and rat bioassays, submitted in this NDA, do not appear to have been submitted to the Canadian Authorities.

In reply to another question, the Sponsor stated that "no carcinogenicity studies were conducted with the metronidazole 10% cream."

The Sponsor's response is satisfactory and no further action on these issues is deemed necessary.

Syed. N. Alam, Ph.D.
Pharmacologist

HFD-540/DD/Concur/Wilkin 1/4/97

HFD-540/TL/Concur/Jacobs 1/10/96

cc:
NDA 20-743

HFD-340/

HFD-540/

HFD-540/Pharm/Alam

HFD-540/TLPharm/Jacobs

HFD-540/MO/Ko

HFD-540/Chem/Higgins

HFD-540/CSO/Cintron

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

NDA 20-743.BP (Original Submission, dated 11/13/96)

JAN 4 1997

Drug Name: Noritate^{R} (metronidazole 1% cream)

Category: Antibacterial, antiprotozoal, antiinflammatory

Indication: Treatment of rosacea including papules, pustules and erythema

Route of Administration: Topical (dermal)

Sponsor: Dermik Laboratories, Inc., Collegeville, PA

Number of Vols.: 5

Date CDER Received: 11/14/96

Date Assigned: 11/19/96

Date Review Started: 12/19/96

Date 1st Draft Completed: 12/26/96

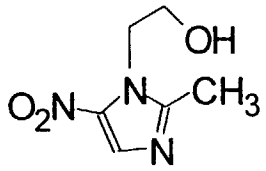
Date Review Accepted by Supervisor:

Related Submissions: IND NDAs 19-737 (0.75% gel), 20-208 (0.75% vaginal gel), 20-531 (0.75% cream), 20-334 (oral capsules)

Review Objective: Summarize the results of two rodent bioassays submitted to determine if metronidazole was carcinogenic in rat and/or mouse.

Chemical Name: 2-Methyl-5-nitroimidazole-1-ethanol

Structure:



Preclinical Studies:

Reviewer's Note: There have been no new pharmacology or toxicology performed with the metronidazole 1% cream. Two animal carcinogenicity studies which the Sponsor (Dermik) believes have not been previously reported, have been included in this NDA application as new studies. was the Sponsor for these studies that were performed at The results are similar to those reported in the literature and to information already included in the labeling for some approved metronidazole preparations. The studies were performed during the period of July 14, 1976 to July 14, 1978, and were not GLP studies. Therefore, these studies are only summarized here. The complete reports were, however, requested for future reference.

1. 2-Year Carcinogenicity Study in Rats: RP 14539 (secnidazole) and RP 8823 (metronidazole) Study # 347-005. Report # 204086 (August, 1980).

Lab Performing Study:

Materials Tested: RP 8823 (metronidazole) and RP 14539 (secnidazole). Only RP 8823 results are summarized here.

Species: Charles River CD rats

Supplier:

Body Weights: Males: 69-214 g. Females: 99-166 g.

Route of Administration: Orally fed in diet

Replacement Group: 5 rats/sex/group were treated in parallel with the study groups. No replacement was done in the metronidazole groups.

Dosage Groups:

Group	Dosage Level mg/kg/day	Test Material	Number of Rats Male	Female	Animal Numbers
I	0 (Control 1)	-	50	50	
II	0 (Control)	-	50	50	
VI	75	RP 8823	50	50	
VII	150	RP 8823	50	50	
VIII	300	RP 8823	50	50	

The animals were observed twice daily for signs of toxicity, morbidity, and mortality. At the end of the study period, all surviving animals were sacrificed and necropsied.

Results:

No overt toxicity was reported. Numerous incidental findings were noted in all groups. There was a dose-related decrease in group mean body weight gain among the treated rats. At the high dose (300 mg/kg/day) the decrease in body weight gain was >10%. The following survival rates at 104 week were reported:

	Males		Females	
Dosage Level	104 Week	% Difference From Control	104 Week	% Difference From Control
0 (Control 1)	31	-	26	-
0 (Control 2)	33	-	31	-
75 RP 8823	27	-15.6	36	+24.1
150 RP 8823	25	-21.9	39	+34.5
300 RP 8823	30	- 6.3	22	-24.1

At the highest dose level, survival was reduced in both sexes, specially in the females.

All groups of rats were observed to have palpable masses (subcutaneous, skin and internal) throughout the study period. Only the high dose (300 mg/kg) females had more palpable masses than the controls. This group also had more multiple masses/rat as compared to controls.

Gross pathology revealed possible compound-related lesions in the livers of both sexes and in the mammary glands in the females.

In this study only the gross lesions were examined microscopically from metronidazole treated rats.

The incidences of various hepatic lesions are shown in the table below.

Group	Hepatocytomegaly		Hepatocellular adenoma		Hepatocellular carcinoma	
	Male	Female	Male	Female	Male	Female
Control I	8	19	4	2	3	1
Control II	10	18	0	1	1	1
VI	6	6	1	3	6	5
VII	12	7	3	6	4	3
VIII	5	5	7	5	15	10

The number of livers examined from each sex of each group were:

Controls: 50 each. 16, 22 and 23 males, and 12, 17 and 15 females from groups VI, VII and VIII, respectively.

The incidence of fibroadenoma in the mammary glands of the high dose females was confirmed during the histopathologic examinations. However, since only the grossly observed changes were examined, the actual incidence could be even higher.

Lung or pituitary adenomas or carcinomas were not increased by metronidazole treatment as

compared to the control animals.

2. Two-Year Carcinogenicity Study in Mice. Study # 347-004. Report #204062.

Lab Performing Study:

Materials Tested: Metronidazole (RP 8823) and Secnidazole (RP 14539).

This study was also initiated and completed between July/1976 and July/1978, and was not performed under GLP guidelines.

All other experimental conditions were similar to the rat study reviewed above.

Dosage Groups:

Group	Compound	Animal Numbers* Males	Females	Dose (Mg/kg/day)
I	Control 1			-
II	Control II			-
VI	RP 8823			75
VII	RP 8823			150
VIII	RP 8823			300

* One control and one each group VI and group VIII animals were replaced later due to untimely death.

Results:

General: No compound-related differences in behavior, appearance and survival were reported between any groups.

The following survival rates were reported:

Compound	Treatment (Mg/kg/day)	No. Surviving/No. Initiated Male	Female
Control 1	0	26/50	27/50
Control 2	0	37/50	24/50
RP 8823	75	31/50	23/50
RP 8823	150	31/50	25/50
RP 8823	300	26/49*	26/50

* Missing animal

Gross Pathology:

Masses/nodules in the liver and lung were reported, but the incidences were similar in the control and the treated groups. Principal oncogenicity findings were of histopathological origin.

Histopathology:

Alveolar cell adenomas characterized by circumscribed proliferation of alveolar cells with compression of the adjacent lung parenchyma and often with focal elevation of the pleural surface were noted in the lungs. The incidences of these lesions in various groups are shown below.

Group	Male	Female
I	15/51	19/50
II	16/50	17/50
VI	21/50	16/51
VII	20/50	19/50
VIII	18/49	20/50

No significant differences between control and treated groups were seen.

However, the total number of lung adenomas was increased in the metronidazole treated male mice in a dose-dependent manner when compared to either of the control groups, although the increases were not statistically significant. Thus, in the various treated male groups, the mean numbers of lung adenomas in affected animals was per group I: 1.1, group II: 1.3, group VI: 1.3, group VII: 1.7 and group VIII: 1.9. In the females, only when compared to the control group 2, there was a dose-related increase in the treated groups. Again, no statistical significance was reported for the increases. But, a correlation coefficient for the metronidazole groups was calculated to be 0.96. It was, therefore, concluded that the increase in multiplicity of lung adenomas was a treatment related effect.

Although a slight increase in alveolar cell carcinoma was seen in the mid-dose group (150 mg/kg), none was reported in the low- (75 mg/kg) and the high-dose (300 mg/kg) groups. No meaningful increases in the hepatocellular adenomas or carcinomas due to metronidazole treatment, were reported in this mouse study. No increased mammary gland tumors due to treatment, were noted . The incidences of mammary gland adenocarcinoma are shown below.

Mammary gland adenocarcinoma

Group	Male	Female
Control 1	-	1
Control 2	-	-
VI (75 mg/kg)	-	2
VII (150 mg/kg)	-	3
VIII (300 mg/kg)	-	1

No increase in pituitary tumors was detected in any group.

Evaluation:

It appears that, of the two imidazole compounds that were assayed simultaneously for their carcinogenicity potential in rodents, the Sponsor put more emphasis on the secnidazole study. Thus, in both the rat and the mouse study with metronidazole, only the gross lesions were examined for histopathology. Obviously, the process invariably would miss many microscopic tissue changes. In addition, none of these studies were performed under GLP guidelines. Therefore, failure to detect any tumors in a particular tissue cannot be accepted as a reason for reclassifying any earlier positive results.

All carcinogenicity studies, other than these two, have been reviewed earlier by Mr. Harold Carlin (IND , Dr. Adeyemo (IND and Dr. Avalos (NDA 20-531 and IND . Their assessment of the results has been incorporated in the labeling of the various approved metronidazole products.

There are now two versions of carcinogenicity labeling for the metronidazole products (PDR) 1995); a short version (Metrogel, Flagyl IV, Metrocream), and a more detailed version (Metrogel vaginal, Flagyl tablets, Protostat^{R} tablets). In this longer version, the fact of increased incidences of liver adenomas and mammary tumors in rats and lung and liver tumors in mice has already been included. The results of the studies reviewed here, do not change the labeling in anyway. Therefore, further biostatistical analysis or CAC deliberation seems unnecessary, especially in view of the deficiencies such as failure to examine all tissues for histopathology and non-adherence to GLP guidelines. The labeling for Metrogel^{R} Vaginal 0.75% is attached for perusal.

Regulatory Recommendation:

The labeling for this metronidazole cream 1% should be similar to that of Metrogel[R] Vaginal 0.75% (see attached).

Recommendation to the Project Manager: This review should be a made a part of the review of the original NDA application.

Syed N. Alam, Ph.D.
Pharmacologist

HFD-540/DD/Concur/Wilkin 1/4/97

HFD-540/TL/Concur/Jacobs 2/27/96

cc:
NDA 20-743

HFD-340/

HFD-540/

HFD-540/Pharm/Alam

HFD-540/TLPharm/Jacobs

HFD-540/MO/Ko

HFD-540/Chem/Vidra

HFD-540/CSO/Cintron