

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-026

PHARMACOLOGY REVIEW(S)

**PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION
Memorandum**

NDA NUMBER: 21-026
SERIAL NUMBER: 000 AZ / 000 BL / 000 BL
DATE RECEIVED BY CENTER: 8-16-2005 / 8-26-2005 / 11-15-2005
DRUG NAME: VUSION Ointment (0.25% miconazole
nitrate, 15% zinc oxide, and 81.35%
white petrolatum ointment)
INDICATION: Diaper dermatitis complicated by
candidiasis
SPONSOR: Barrier Therapeutics, Inc.
REVIEW DIVISION: Division of Dermatologic and Dental
Products (HFD-540)
PHARM/TOX REVIEWER: Jiaqin Yao, Ph.D.
PHARM/TOX SUPERVISOR: Paul C. Brown, Ph.D.
ACTING DIVISION DIRECTOR: Stanka Kukick, M.D.
PROJECT MANAGER: Millie Wright

Date of review submission to Division File System (DFS): 2-6-2006

The sponsor resubmitted an application (N-000 AZ) in response to the Non-Approvable Letter dated May 24, 2005. The NDA was previously found to be approvable from a Pharmacology/Toxicology perspective and the submissions do not include any new nonclinical studies. Therefore, this NDA is approvable from a Pharmacology/Toxicology perspective and no additional nonclinical studies are recommended at this time.

Recommendations for the labeling:

Carcinogenesis, Mutagenesis, Impairment of fertility: Studies to evaluate the carcinogenic potential of VUSION Ointment in animals have not been performed.

Miconazole nitrate was negative in a bacterial reverse mutation test, a chromosome aberration test in mice, and micronucleus assays in mice and rats.

Miconazole nitrate had no adverse effect on fertility in a study in rats at oral doses of up to 320 mg/kg/day, which is 89 times the maximum possible topical exposure of caregivers, assuming 100% absorption.

Pregnancy Category C:

There are no adequate and well-controlled studies of VUSION Ointment in pregnant women. Miconazole nitrate administration has been shown to result in prolonged gestation and decreased numbers of live young in rats and in increased number of resorptions and decreased number of live young in rabbits at oral doses of 100 mg/kg/day and 80 mg/kg/day, which are 28 and 45 times the maximum possible topical exposure of caregivers, respectively, assuming 100% absorption.

Pregnant women should exercise appropriate precautions when administering the product.

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

cc: list:

HFD-540/CSO/WrightM

HFD-540/Pharm. Sup./BrownP

HFD-540/MO/CarrB

FD-540/TL/LukeM

HFD-540/ADD/KukichS

**Appears This Way
On Original**

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

/s/

Jiaqin Yao
2/6/2006 10:02:50 AM
PHARMACOLOGIST

Paul Brown
2/6/2006 04:57:45 PM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION
Memorandum

NDA NUMBER: 21-026
SERIAL NUMBER: 000 AZ
DATE RECEIVED BY CENTER: 11/24 /2004
DRUG NAME: ZIMYCAN (Miconazole nitrate 0.25% ointment)
INDICATION: Diaper dermatitis complicated by candidiasis
SPONSOR: Barrier Therapeutics, Inc.
REVIEW DIVISION: Division of Dermatologic and Dental Drug Products (HFD-540)
PHARM/TOX REVIEWER: Jiaqin Yao, Ph.D.
PHARM/TOX SUPERVISOR: Paul C. Brown, Ph.D.
DIVISION DIRECTOR: Jonathan Wilkin, M.D.
PROJECT MANAGER: Millie Wright

Date of review submission to Division File System (DFS): 3-30-2005

The sponsor resubmitted this application in response to the Non-Approvable Letter dated July 24, 2000. The NDA was previously found to be approvable from a Pharmacology/Toxicology perspective and this current submission does not include any new nonclinical studies. Therefore, this NDA is approvable from a Pharmacology/Toxicology perspective and no additional nonclinical studies are recommended at this time.

The following information regarding labeling is adapted from that previously recommended by Dr. Amy Nostrandt in Review 2 of this NDA finished on April 14, 2000.

1. Add a warning against use of the product on open wounds under **PRECAUTIONS**.

2. The ocular irritation study referenced in the original NDA was performed with an alternative formulation of the drug product. It is not accurate to state that the to-be-marketed formulation is not an ocular irritant when it specifically has not been tested for

that property. Consider the following changes, under **PRECAUTIONS, General:**

b(4)

Avoid introduction of ZIMYCAN Ointment into the eyes.

3. The sponsor has rights of reference to some genetic and reproductive/developmental toxicity studies of miconazole. Results from the following studies along with others should be added into the labeling. As Dr. Amy Nostrandt stated in her previous review, "In phase 3 trials, the reported average use was 38.69 g of ointment in one week (approximately 13.8 mg miconazole per day). The average patient body weight was 7.9 kg, resulting in an average daily dose of 1.75 mg/kg/day. The applicant states that at maximum usage the total daily dose is 4.52 mg/kg/day." Therefore, the total daily amount of miconazole at the maximum usage was 35.7 mg/day (4.52 mg/kg/day \times 7.9 kg). Since the drug will be administered to children by caregivers who may be pregnant or nursing and could be exposed to the drug, the value of 0.60 mg/kg/day (35.7 mg/day \div 60 kg) is used as the maximum possible human exposure for comparison between animal doses in reproductive/developmental toxicity studies and human topical exposure.

3.1. Miconazole did not induce an increase of micronucleated polychromatic and normochromatic erythrocytes in micronucleus assays conducted in mice treated orally with up to 640 mg miconazole/kg (HED = 53.3 mg/kg) and in rats treated intraperitoneally with up to 320 mg miconazole/kg (HED = 53.3 mg/kg).

3.2. No adverse effects on fertility were reported in a segment I study conducted in rats at oral doses up to 320 mg/kg/day (HED = 53.3 mg/kg/day, which is 89 times the maximum possible topical exposure of caregivers, assuming 100% absorption).

3.3. Increased duration of gestation and decreased number of live pups were reported in rats orally receiving 100 mg miconazole nitrate/kg/day (HED = 16.7 mg/kg/day, which is 28 times the maximum possible topical exposure of caregivers, assuming 100% absorption). An increased number of resorptions and decreased number of live pups were reported in rabbits orally receiving 80 mg miconazole nitrate/kg/day (HED = 26.7 mg/kg/day, which is 45 times the maximum possible topical exposure of caregivers, assuming 100% absorption).

Recommendations for the labeling:

1. Under **PRECAUTIONS**, add a warning against use of the product on open wounds.

2. Under **PRECAUTIONS, General:**

Avoid introduction of ZIMYCAN Ointment into the eyes.

b(4)

3. Add **Carcinogenesis, mutagenesis, impairment of fertility:** Studies to evaluate the carcinogenic potential of ZIMYCAN in animals have not been performed.

Miconazole was negative in a test for gene mutation in *Salmonella typhimurium* strains TA100 and TA98. Miconazole was also negative in micronucleus assays in mice and rats administered up to a human equivalent dose of 53 mg/kg orally or intraperitoneally, respectively. Miconazole was negative in a chromosome aberration test in mice and in a dominant lethal test in male and female mice. Evaluation of miconazole in an in vitro plate incorporation test and in an in vivo sex-linked recessive lethal test also yielded negative results. In an in vitro non-disjunction test in the fungus *A. nidulans*, an increase in the number of abnormal and non-disjunctional colonies was observed at cytotoxic dose levels. The relevance of the latter test to mammals is unknown.

Miconazole had no adverse effect on fertility in a study in rats at oral doses of up to 320 mg/kg/day, which is 89 times the maximum possible topical exposure of caregivers, assuming 100% absorption.

4. Under Pregnancy: Pregnancy Category C:

Miconazole nitrate administration has been shown to result in prolonged gestation and decreased numbers of live young in rats and in increased number of resorptions and decreased number of live young in rabbits at oral doses of 100 mg/kg/day and 80 mg/kg/day, which are 28 and 45 times the maximum possible topical exposure of caregivers, respectively, assuming 100% absorption. There are no adequate and well-controlled studies of ZIMYCAN in pregnant women.

5. Under Nursing Mothers: It is not known if ZIMYCAN may be present in milk. Appropriate precautions should be followed when administering the product.

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

cc: list:

HFD-540/CSO/WrightM
HFD-540/Pharm. Sup./BrownP
HFD-540/MO/CarrB
FD-540/TL/LukeM
HFD-540/DDD/KukichS
HFD-540/DD/WilkinJ

**Appears This Way
On Original**

b(4)

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

/s/

Jiaqin Yao
3/30/05 08:40:39 AM
PHARMACOLOGIST

Paul Brown
3/30/05 04:55:42 PM
PHARMACOLOGIST

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: miconazole, diaper dermatitis, Pediastat®
Reviewer Name: Amy Nostrandt
Division Name: Division of Dermatologic and Dental Drug Products HFD# 540 MAR 23 2000
Review Completion Date: 4/14/00

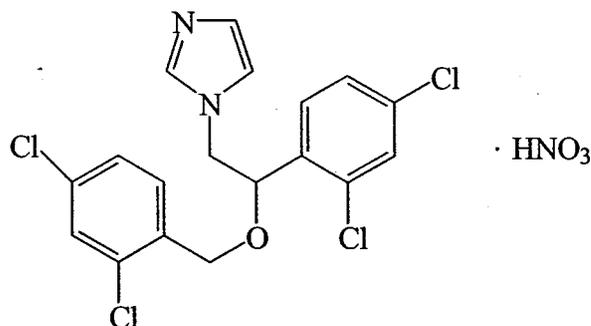
Review number: 2
IND/NDA number: NDA 21-026
Serial number/date/type of submission: BL, received 3/29/00, proposed product insert to accompany NDA resubmission

Information to sponsor: Yes () No (X)
Sponsor (or agent): Johnson & Johnson Consumer Companies, Inc.
Manufacturer for drug substance: not specified in this submission

Drug:

Code Name: R14,889
Generic Name: 0.25% miconazole nitrate
Trade Name: Pediastat™ (0.25% miconazole nitrate) Diaper Rash Ointment
Chemical Name: 1H-Imidazole, 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-mononitrate; 1-[2,4-dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl]imidazole mononitrate
CAS Registry Number: 22832-87-7
Molecular Formula/ Molecular Weight/Structure:

$C_{18}H_{14}Cl_4N_2O \cdot HNO_3$
MW = 479.15



Relevant INDs/NDAs/DMFs:

IND 21,542 miconazole nitrate ointment
Johnson & Johnson Consumer Companies, Inc.
0.25% miconazole nitrate ointment
Johnson & Johnson Consumer Companies, Inc.

NDA 17-450 MONISTAT 7 vaginal cream Advanced Care Products
NDA 17-494 MONISTAT-DERM Cream 2% miconazole nitrate
Johnson & Johnson Consumer Companies, Inc.
NDA 18-040 MONISTAT injectable solution Janssen Pharmaceutica, Inc.
NDA 18-520 MONISTAT 7 vaginal suppositories Advanced Care Products

b(4)

Drug Class: imidazole antifungal

Indication: diaper dermatitis

Clinical formulation: Formula #610-73 (vehicle 610-115)

<u>Component</u>	<u>%w/w</u>	<u>role</u>
miconazole nitrate, USP	0.25	active
zinc oxide, USP	15.00	vehicle
white petrolatum, USP	81.35	vehicle
(Chemoderm 1001/B)		fragrance
trihydroxystearin		

b(4)

Total 100.00

Route of administration: topical to the skin

Proposed clinical protocol or Use: The proposed label directs that the drug product should be applied to the entire affected area at each diaper change after cleansing and drying. Treatment is recommended to be continued until there are no longer signs of irritation or for a maximum of seven days.

Previous clinical experience: In a pharmacokinetics study involving seven days of application at each diaper change, drug levels were measurable in 3/18 infants (approximately 20% of subjects) treated with multiple daily doses of 0.25% miconazole nitrate ointment. Serum levels were between 3.0-3.8 ng/mL (LOD=1 ng/ml) in those subjects.

The applicant reports that there is little potential for dermal toxicity or irritation with this product. Out of 252 infants treated with 0.25% miconazole nitrate ointment, the applicant reports that there was only one drug-related adverse event. The applicant also reports that in post-marketing surveillance for the OTC product marketed abroad there were two possibly drug-related adverse events.

The applicant estimates that diaper dermatitis should be limited to about eight episodes during the first two to three years of life, with an average duration of three days per episode. They state that even though a severe episode could take as much as ten days to resolve, use of the drug product would not be chronic. This estimate does not take into account exposures to the drug substance later in life for treatment of dermatophytoses, etc.

The drug product is marketed for this indication in several European countries. It was disapproved in Norway because of concerns related to topical absorption in infants and development of resistant organisms.

Disclaimer : Note that some information may come directly from the sponsor's submitted material.

Introduction and drug history:

A nonapprovable letter was issued for the original NDA for this product on 6/28/99. A full response was submitted to the chemistry and clinical issues on 1/21/00. The current submission consists of proposed labeling for the drug product. Recommendations were made for

those portions of the label relevant to pharmacology and toxicology in the review of the original NDA. Those recommendations are modified somewhat below.

Studies reviewed within this submission: No studies were submitted.

Studies not reviewed within this submission: none

PHARMACOLOGY:

Summary of pharmacology:

Miconazole is an imidazole antifungal agent. This class of drugs act to inhibit sterol biosynthesis, specifically the synthesis of ergosterol, a component of the fungal cytoplasmic membrane. The function of the cytoplasmic membrane and membrane-associated enzyme systems may be impaired and growth is inhibited.

SAFETY PHARMACOLOGY:

Summary:

Safety pharmacology studies were conducted to investigate effects on the nervous system, cardiovascular system, and digestive system. Findings in neuropharmacology studies were unremarkable. In cardiovascular studies in multiple species, the Q-T interval of the ECG was prolonged, and increased sensitivity to induction of ventricular fibrillation after epinephrine challenge was noted. In studies of effects on the gastrointestinal tract, antagonism of spasmogens was noted, as was non-competitive antagonism of histamine. Neither anticholinergic activity nor β -adrenergic blockade were observed.

PHARMACOKINETICS/TOXICOKINETICS:

Summary:

ADME studies demonstrated low absorption of miconazole after dermal application. Drug distribution was primarily to liver, kidney, lung, adrenal, and thyroid after topical administration. In vitro, miconazole was >90% bound to plasma proteins (primarily albumin) in human blood. Miconazole is highly metabolized in man and animals. It is excreted primarily in the bile, with enterohepatic recirculation. Smaller amounts of metabolites are excreted in urine.

TOXICOLOGY:

General Comments: Nonclinical studies to support the safety of miconazole nitrate have been previously reviewed.

Overall Toxicology Summary:

Studies of a 0.25% miconazole nitrate ointment that is nearly identical to the proposed drug product include acute oral toxicology in the mouse and rat, acute dermal toxicology in rabbits, and dermal and ocular irritation studies in rabbits. No mortality was seen in acute oral studies at doses in mice and rats equivalent to human doses of 8.3 and 6.25 mg/kg, respectively. Observations included slight decreases in activity, body tone and righting reflex and slight diarrhea. In the acute dermal toxicity study, effects were limited to edema at the treatment site after 24 hour occlusion of a dose equivalent to 1.7 mg/kg in humans.

Oral and intravenous studies of miconazole in rats, rabbits, and beagle dogs have demonstrated that the liver is the target organ of toxicity. NOEL's were 5.5 mg/kg/day po in rats for 78 weeks (HED = 0.92 mg/kg/day, or 0.2 times the maximum clinical daily dose), 5 mg/kg/day iv in rabbits for 6 months (HED = 1.7 mg/kg/day, or 0.4 times the maximum clinical

daily dose), and 5 mg/kg/day po in dogs for 52 weeks (HED = 2.5 mg/kg, or 0.55 times the maximum clinical daily dose). A six-month dermal toxicology study in rabbits revealed local effects at the treatment site only. The NOEL for that study was 40 mg/kg/day (HED = 13 mg/kg/day, or three times the maximum clinical daily dose).

CARCINOGENICITY:

No carcinogenicity studies were submitted.

IMMUNOTOXICOLOGY:

No immunotoxicology studies were submitted.

REPRODUCTIVE TOXICOLOGY:**Summary:**

In reproductive and developmental toxicology testing, miconazole did not appear to have effects on fertility or teratogenicity. In the rat, at doses equivalent to 16.7 mg/kg in the human, the duration of gestation was increased and the number of live pups was decreased. In the rabbit, at doses equivalent to human doses of 26.7 mg/kg, resorptions were increased and the number of live pups was decreased. Segment 3 studies in rats and rabbits demonstrated decreases in pup body weights and decreased pup survival.

Labeling Recommendations: The drug is indicated for pediatric use. However, the drug may be administered by caregivers who may be nursing or pregnant, so precautionary statements are recommended below.

GENETIC TOXICOLOGY:**Summary:**

Miconazole was negative for genotoxicity in most studies, although the concentrations used may not have been adequately high. Miconazole was positive for genotoxicity in the non-disjunction test in *Aspergillus nidulans*.

SPECIAL TOXICOLOGY STUDIES:**Summary:**

Miconazole nitrate ointment was a mild to moderate skin irritant and was not an ocular irritant in irritation studies in rabbits.

OVERALL SUMMARY AND EVALUATION:

Introduction: The original NDA for Pediastat™ was approvable from the standpoint of pharmacology and toxicology. Recommendations are made for relevant portions of the label.

Safety Evaluation: Systemic exposures in rats at oral doses similar to those producing liver toxicity were approximately 4 µg/mL in plasma. At a dose near the NOEL in the oral study in rats, C_{max} was 0.6 µg/ml.

Clinical Relevance of Safety Issues: In some infants in clinical trials, plasma levels were measurable and were 3-4 ng/ml. This would seem to indicate a relative margin of safety of two orders of magnitude in patients under conditions of short-term treatment.

Other Clinically Relevant Issues: none

Conclusions: From a pharmacology/toxicology standpoint, the application is approvable, with the following label revisions.

Communication Review:

- Labeling Review (NDA): The following recommendations are made for the portions of the label relevant to pharmacology and toxicology:

1. Under **CLINICAL PHARMACOLOGY**, the review team may wish to consider mention of hepatic metabolism of miconazole in man and animals.
2. Under **PRECAUTIONS**,
 - a. The Belgian label warns against use of the product on open wounds. The review team may wish to consider a similar statement.

b. **General:** ...

Avoid introduction of PEDIASSTAT™ into the eyes.

Reviewer's comment: The ocular irritation study referenced in the original NDA was performed with an alternative formulation of the drug product. It is not accurate to state that the to-be-marketed formulation is not an ocular irritant when it specifically has not been tested for that property.

c. The following section should be added:

Carcinogenesis, mutagenesis, impairment of fertility: Studies to evaluate the carcinogenic potential of PEDIASSTAT in animals have not been performed.

Miconazole was negative in a test for gene mutation in *Salmonella typhimurium* strains TA100 and TA98. Miconazole was also negative in micronucleus assays in mice and rats administered up to a human equivalent dose of 53 mg/kg orally or intraperitoneally, respectively. Miconazole was negative in a chromosome aberration test in mice and in a dominant lethal test in male and female mice. Evaluation of miconazole in an in vitro plate incorporation test and in an in vivo sex-linked recessive lethal test also yielded negative results. In an in vitro non-disjunction test in the fungus *A. nidulans*, an increase in the number of abnormal and non-disjunctional colonies was observed at cytotoxic dose levels. The relevance of the latter test to mammals is unknown.

Miconazole had no adverse effect on fertility in a study in rats at oral doses up 100 times the human topical exposure, assuming 10% bioavailability of the topical product.

d. The **Pregnancy/Nursing Mothers** section should be modified, since the drug will be administered by caregivers who may be pregnant or nursing and could be exposed to the drug, as follows:

Pregnancy/Nursing Mothers: Safety and efficacy of the product have not been established in pregnant women. Miconazole nitrate administration has been shown to result in prolonged gestation and decreased numbers of live young in rats and in increased number of resorptions and decreased number of live young in rabbits at oral doses 33 and 53 times the human topical exposure, respectively, assuming 10% bioavailability. There are no adequate and well-controlled studies of PEDIASSTAT in pregnant women. It is not known if PEDIASSTAT may be present in milk. Appropriate precautions should be followed when administering the product.

b(4)

- 3. Under **OVERDOSAGE**, the review team may wish to consider addition of information to describe acute oral toxicity studies, to identify the liver as the target organ of toxicity, and to describe possible increased sensitivity to catecholeamines seen in animal cardiovascular pharmacology studies.

- Investigator's Brochure/Informed consent review (IND): not applicable

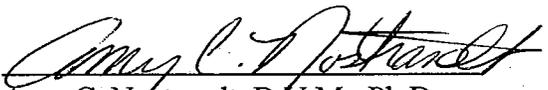
RECOMMENDATIONS:

Internal comments: From a pharmacology/toxicology standpoint, the application is approvable, with the above label revisions.

External Recommendations (to sponsor): The revised label developed by the review team will be forwarded to the sponsor, pending approvability of the application.

Draft letter Content for Sponsor: not applicable

Future development or NDA issues: not applicable


 Amy C. Nostrandt, D.V.M., Ph.D. 5/17/00
 Pharmacologist/Toxicologist

cc:

NDA 21-026

HFD-340

HFD-540

HFD-540/PHARM/Nostrandt

HFD-540/TLPHARM/Jacobs

HFD-540/MO/Ko

HFD-540/CHEM/Timmer

HFD-540/PMS/Wright

C:\word files\nda\n21026_BL_3_29_00.doc

Draft date (# of drafts): 4/14/00 (1)

Concurrence Only:

HFD-540/DD/WILKIN  5/25/00 DFS

HFD-540/TLPHARM/JACOBS  5/23/00 IN DFS

**Appears This Way
 On Original**

Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products, HFD-540

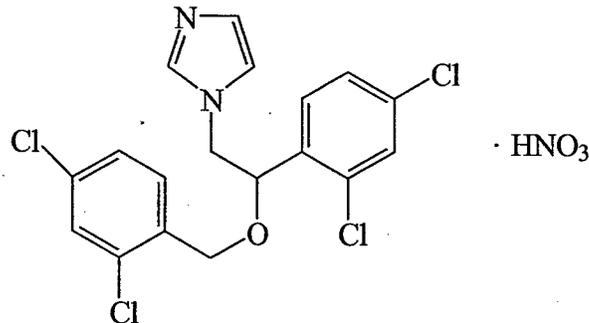
NDA No.: 21-026

MAY 5 1999

Date Submitted: 8/24/98
Date CDER Received: 8/24/98
Date Assigned: 8/28/98
Date Review Completed: 4/28/99

Name of Drug: PEDIASTAT™ (0.25% miconazole nitrate) Diaper Rash Ointment;
1H-Imidazole, 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)
methoxy]ethyl]-mononitrate; 1-[2,4-dichloro-β-[(2,4-dichlorobenzyl)
oxy]phenethyl] imidazole mononitrate; R14,889
CAS Number – 22832-87-7

Structure:



Molecular Weight: 479.15
Molecular Formula: $C_{18}H_{14}Cl_4N_2O \cdot HNO_3$

UV Absorption: not provided in volumes for pharmacology review

Pharmacological Category: imidazole antifungal agent

Sponsor: Johnson & Johnson Consumer Companies
199 Grandview Road
Skillman, NJ 08558-9418

Indication: diaper dermatitis

Route of Administration: topical to the skin

Formulation: Formula #610-73	(vehicle 610-115)	
<u>Component</u>	<u>%w/w</u>	<u>role</u>
miconazole nitrate, USP	0.25	active
zinc oxide, USP	15.00	vehicle
white petrolatum, USP	81.35	vehicle
(Chemoderm 1001/B)		fragrance
trihydroxystearin		
Total	100.00	

b(4)

Related IND's/NDA's:

IND 21,542 miconazole nitrate ointment
 Johnson & Johnson Consumer Companies, Inc.
 0.25% miconazole nitrate ointment
 Johnson & Johnson Consumer Companies, Inc.

b(4)

NDA 17-450 MONISTAT 7 vaginal cream Advanced Care Products
 NDA 17-494 MONISTAT-DERM Cream 2% miconazole nitrate
 Johnson & Johnson Consumer Companies, Inc.
 NDA 18-040 MONISTAT injectable solution Janssen Pharmaceutica, Inc.
 NDA 18-520 MONISTAT 7 vaginal suppositories Advanced Care Products

Index of Nonclinical Studies:

Pivotal Nonclinical Toxicology studies (reviewed previously):

<u>study report #</u>	<u>title</u>	<u>previously submitted and reviewed under:</u>
7336/10841.50C	The acute oral toxicity of diaper rash ointment formula no. 610-58 in the albino mouse	
7336/10841.50A	The acute oral toxicity of diaper rash ointment formula no. 610-58 in the albino rat	
7336/10841.51	The acute dermal toxicity of diaper rash ointment formula no. 610-58 in the rabbit	
284	Eighteen month chronic oral drug safety study in male and female rats with 26 and 52 week interim sacrifices.	NDA 17-450
---	Subacute (six month) dermal toxicity study in rabbits	NDA 17-450
706 (N13703)	Intavenous toxicity study in New Zealand White rabbits (repeated dosage for six months)	NDA 18-040
316	A 52-week chronic oral drug safety study in male and female beagle dogs. September 1971.	NDA 17-450
7336/10841.57	A primary dermal irritation study of diaper rash ointment formula no. 610-58 in the albino rabbit	
DS-6043	Vaginal irritation study (10 days) of ORF 7370	

b(4)

b(4)

	4% creams in rabbits. September 2, 1986.	
---	Twelve day subacute vaginal irritation and toxicity study in female rabbits. September, 1971	NDA 17-450
---	Twenty-eight day intravaginal subacute drug safety study in female rabbits. March, 1975.	NDA 18-520
---	Three-month intravaginal subacute drug safety study in female rabbits	NDA 17-450
---	Three month intravaginal subacute irritation test in female monkeys. December, 1970.	NDA 17-450
7336/10841.56B	An ocular irritation study of 0.25% diaper rash ointment formula 610-58 in the albino rabbit	
2074 (N64925)	Micronucleus tests in rats or mice	NDA 18-040
999 (N22029)	Micronucleus tests in rats	NDA 18-040
966 (N21035)	Dominant lethal test in male mice	NDA 18-040
984 (N21471)	Dominant lethal test in female mice	NDA 18-040

b(4)

Pivotal Nonclinical Toxicology studies not previously submitted and reviewed in this submission:

1. Study no. DS-5050: Vaginal irritation study (10 days) of miconazole 4% cream in rabbits. May, 1986
2. Study no. N11660: Studies on miconazole (Report 8) – Toxicological mutagenicity tests of miconazole.
3. Voogd CE and Van derStel JJ. Are econazole, miconazole (R14889) and clotrimazole mutagenic to bacteria? Mutation Research 120:91-95, 1983.
4. Bellincampi D et al. Membrane damaging agents cause mitotic non-disjunction in *Aspergillus nidulans*. Mutation Research 79:169-172, 1980.

Pharmacokinetic Studies:

summary of previously reviewed studies and literature citations

Nonclinical Pharmacology Studies

summary of previously reviewed studies

INTRODUCTION

The applicant suggests that there is potential for *Candida albicans* to colonize irritated skin in infants with diaper dermatitis, resulting in worsening of the condition. The drug substance, miconazole, is active against that organism and may improve the condition and speed healing. The applicant states that, currently, treatment of diaper dermatitis includes prescriptions for off-label use of topical steroids or antifungal/steroid combinations and suggests that this product would be a better alternative to the use of topical steroids in infants.

Topical miconazole is approved for use in the treatment of dermatophytoses and vulvovaginal candidiasis in several OTC products.

The applicant states that the recommended clinical use of the product is to apply the drug product to the affected area at each diaper change. In phase 3 trials, the reported average use was 38.69 g of ointment in one week (approximately 13.8 mg miconazole per day). The average

patient body weight was 7.9 kg, resulting in an average daily dose of 1.75 mg/kg/day. The applicant states that at maximum usage the total daily dose is 4.52 mg/kg/day. This value is used below to calculate dose multiples for comparison between animal studies and human clinical use.

NONCLINICAL TOXICOLOGY STUDIES

The applicant refers to and summarizes the studies previously submitted for the drug substance in approved products. Additionally, acute studies (oral toxicology, dermal toxicology, dermal and ocular irritation) were performed with a formulation similar to the to-be-marketed formulation that were submitted and reviewed. Those studies were conducted with formulation 610-58, which is identical to the to-be-marketed formulation except that the fragrance component (Chemoderm 1001) contained this was later removed. The resulting formulation of the fragrance was Chemoderm 1001/B. Most of the other toxicology studies were performed using Monistat 7 cream, which has the following formulation:

b(4)

<u>ingredient</u>	<u>%</u>
purified water, USP	99.8
miconazole nitrate	2.0
benzoic acid, USP	
<hr/>	
Total	100.0%

b(4)

In the studies summarized below, the applicant frequently states the dose of the active ingredient as being slightly higher than would be calculated based on percent formulation. In one case, a vaginal suppository is described as a product containing 20 mg miconazole nitrate, yet the dose is described as 23 mg miconazole nitrate. It is unclear if the formulation includes overage or how the applicant is otherwise arriving at conflicting doses. In the review below, doses are what the reviewer has calculated based on the percent formulation, or, in the second case, a 20 mg miconazole nitrate suppository is reviewed below as containing a 20 mg miconazole nitrate dose.

General Toxicology Studies:

An acute oral dose of 40 g/kg (HED= 3.3 g/kg) of 0.25% miconazole nitrate ointment (100 mg/kg miconazole nitrate; HED= 8.3 mg/kg), formulation 610-58, in Swiss Webster albino mice (5/sex) resulted in no mortality after a seven-day observation period. Observed signs included slightly decreased activity in one male and slight diarrhea in one female.

In an acute oral study in Sprague Dawley albino rats (5/sex), 15 g/kg (HED= 2.5 g/kg) of 0.25% miconazole nitrate ointment (37.5 mg/kg miconazole nitrate, HED= 6.25 mg/kg), formulation 610-58, no drug-related deaths were reported during the seven-day observation period. Clinical signs were noted in one male and two females and consisted of slightly decreased activity and body tone, slightly reduced startle response and slight loss of righting reflex.

From the review of NDA 17-494, the acute oral LD₅₀'s for 2% miconazole nitrate cream were 40 ml/kg in mice and rats and 8 ml/kg in newborn rats. In the review of NDA 18-040, the LD₅₀'s for intravenously administered miconazole base were 98.5 mg/kg in male rats, 44.0 mg/kg in guinea pigs, and 62.5 mg/kg in beagle dogs.

An acute dermal toxicology study was performed in NZW rabbits (5/sex/group). One group served as a sham control, and the treated group had 2 g/kg (HED= 0.67 g/kg) of 0.25% miconazole nitrate ointment (5 mg/kg miconazole nitrate, HED= 1.7 mg/kg), formulation 610-58, applied topically to shaved areas of skin on the trunk. The treatment site was occluded for 24 hours, and animals were observed for two weeks. Severe edema was seen at test article treated sites on day one. By the end of the study, this had subsided to slight edema and was resolved in three animals. There was no evidence of systemic toxicity.

Multiple dose studies were performed in rabbits (dermal and iv), rats (oral) and dogs (oral). In oral and intravenous studies, the liver was the target organ of toxicity, with effects seen at the higher doses.

A 78-week chronic oral toxicology study was performed in Wistar rats (30/sex/group) with interim sacrifices at 26 and 52 weeks (10/sex/group at each interval). Test article was administered in the diet; average daily doses of miconazole were 5.5-7.8 mg/kg for the low dose group, 23.6-30.6 mg/kg for the mid-dose group, and 83.4-123.2 mg/kg for the high dose group (provided text and tables are not in agreement regarding these values; these values are from the tabulated summaries). An untreated group served as the control. No drug-related effects were noted on mortality, clinical observations, hematology, clinical chemistry, or gross pathology. Food consumption was decreased in all treated males and in high dose females at the 26-week interval, and in mid- and high dose females and high dose males at the 52-week interval. During the 78-week interval, food consumption was similar in treated and control groups. Mean body weights were lower in high dose females at both interim sacrifices, but not at 78 weeks. Relative liver weights were increased in high dose animals at all three sacrifices. Histologically, the livers of high dose animals were found to have centrilobular cloudy swelling and/or fatty surcharge with vacuoles and occasional hyaline degeneration of some hepatocytes. Similar lesions were seen at the mid-dose, at lesser severity and incidence. Liver changes were more marked at the 26-week sacrifice than at the later ones and were more pronounced in males than females. The applicant states that these changes were considered reversible. The NOEL in this study was 5.5 mg/kg/day (HED= 0.92 mg/kg/day, or 0.2 times the maximum clinical daily dose).

A six-month dermal toxicology study was performed in albino rabbits (6/sex/group) with a three-month interim sacrifice. Doses of 2% miconazole nitrate cream were 0.2, 1, or 2 g/kg/day (HED= 0.067, 0.33, or 0.67 g/kg/day), or 4, 20, or 40 mg miconazole nitrate/kg/day (HED= 1.3, 6.7, or 13 mg/kg/day), administered topically for five days per week. A control group received a placebo formulation. Early local effects seen in the test and placebo groups included considerable erythema, loss of skin elasticity, and drying and cracking of the skin. These signs subsided after approximately one week, and local effects were limited thereafter to slight erythema, slight loss of skin elasticity, and slight hyperkeratosis. Local effects were similar in all test and placebo groups. No effects of the drug were seen on results of hematology, clinical chemistry, gross necropsy, organ weights, and histological examination. The NOEL for systemic toxicity was determined to be 40 mg/kg/day (HED= 13 mg/kg/day, or approximately 3 times the maximum clinical daily dose).

A six-month intravenous toxicology study of 1% miconazole solution was conducted in NZW rabbits (3/sex/group) at doses of 5, 10, or 20 mg/kg/day. A placebo group was included. Dosing was once daily, for six days per week. According to the applicant, no treatment-related effects were seen on mortality, clinical observations, body weights, hematology, serum chemistry, or gross pathological examination. The review of NDA 18-040 states that BUN was slightly increased in high dose animals and that serum glucose, ALT, and AST were slightly increased in mid- and high dose animals. Local effects included transitory thickening of the injected ear. Histological changes were noted in the liver, spleen, adrenals, and larger blood vessels of the lungs in control and treated animals and were judged to be not drug-related. Additionally, fatty degeneration of the liver, concomitant with glycogen depletion, was found in animals in mid- and high dose groups. The NOEL was reported by the applicant to be 20 mg/kg/day of miconazole (HED= 6.7 mg/kg/day, 1.5 times the maximum clinical daily dose). Based on the clinical chemistry findings and the fatty degeneration of the liver in mid- and high dose groups, it may be more accurate to state that the NOEL was 5 mg/kg/day (HED= 1.7 mg/kg/day, 0.4 times the maximum clinical daily dose).

A 52-week oral toxicology study was performed in beagle dogs (3/sex/group). Capsules containing miconazole nitrate were administered orally six days per week. Doses were 1.25, 5, or 20 mg/kg/day (HED= 0.625, 2.5, or 10 mg/kg/day). A placebo group was included. No treatment-related effects were seen on mortality, clinical observations, body weights, hematology, ECG, or indirect blood pressure. Serum chemistry alterations consisted of a persistent increase in serum alkaline phosphatase and AST [The review of NDA 17-450 states that the increase was in SGPT (ALT)] activities at the high dose. An increase in relative liver weight was seen at the high dose, but no gross or microscopic pathological changes were noted in any organ system, including the liver. The NOEL was determined to be 5 mg/kg/day (HED= 2.5 mg/kg/day, or 0.55 times the maximum clinical daily dose).

Special Toxicology Studies:

Special toxicology studies addressed local effects on the skin, eye, and vaginal tissue. When 0.5 mL of 0.25% miconazole nitrate ointment (formulation 610-58) was applied to intact and abraded skin of rabbits, it was considered to be a mild dermal irritant, although the irritation score was very near moderate. In the same study, white petrolatum and distilled water were moderate and mild irritants, respectively. A single dose of 0.1 mL (0.25 mg) of 0.25% miconazole nitrate ointment (formulation 610-58) was not an ocular irritant in rabbits. Vaginal formulations administered to rabbits and monkeys did not result in any systemic toxicity. Locally, one mL of 4% miconazole nitrate cream (40 mg miconazole) applied once daily for 10 days in two studies resulted in mild to moderate irritation of rabbit vaginal mucosa, while mild irritation was seen in sham control animals. In a 12-day vaginal irritation/tox study in rabbits, one mL of 2% miconazole nitrate cream/day (20 mg miconazole nitrate/day) resulted in no drug-related toxicity and no differences between control and treated animals. A 28-day intravaginal safety study was conducted in NZW rabbits (20/group) using 1 g vaginal suppositories containing 40 mg miconazole nitrate. No effects were noted on clinical observations, clinical chemistry or hematology, or ophthalmologic toxicity. Absolute and relative pituitary gland weights were lower in treated animals than in placebo-treated controls, but there were no corresponding histopathologic lesions. Mild vaginal irritation was seen in both treated and control groups. In a 90-day intravaginal irritation study in NZW rabbits (10/group), one g

vaginal suppositories with 20 mg miconazole nitrate cream in a carbowax vehicle or with vehicle only were administered daily. Hematology, clinical chemistry, urinalysis, and ophthalmologic data were within normal limits. The mean relative myocardial weights in treated animals were significantly lower than controls. Microscopic evaluation of the vaginal mucosa revealed mild to marked irritation in treated animals and mild irritation in controls. (*Reviewer's comment: The severity of irritation was described in the summary table for this study as above and is in agreement with an earlier review, but at least one text description described irritation as mild to moderate in test animals and very mild in controls.*) A 12-week intravaginal irritation study was conducted in cynomolgus monkeys. Four animals were administered 1 g vaginal suppositories containing 20 mg miconazole nitrate once daily for 90 days, or approximately 5 mg/kg/day (HED = 1.7 mg/kg). No treatment-related effects were noted on clinical observations, body weight, hematology, clinical chemistry, ophthalmologic examinations, or organ weights. Histological examination revealed a mild increase in vaginal squamous epithelial thickness in both control and treated groups that was slightly more pronounced in treated animals.

Genotoxicity:

An in vitro test for gene mutation in bacteria was conducted in *Salmonella typhimurium* strains TA100 and TA98 with and without metabolic activation. Cultures were exposed to 0.1-200 mg/L miconazole. There was no increase in the number of revertants under any of the above conditions.

A micronucleus assay was conducted in mice treated orally with 40, 160, or 640 mg miconazole/kg (HED= 3, 13, or 53 mg/kg, respectively). A second assay was conducted in rats treated intraperitoneally with 20, 80, or 320 mg miconazole/kg (HED= 3, 13, or 53 mg/kg, respectively). Miconazole did not induce an increase of micronucleated polychromatic and normochromatic erythrocytes in either test.

A chromosome aberration test was conducted in mice administered 650 mg miconazole/kg orally or 170 mg miconazole/kg ip (HED= 54 or 14 mg/kg, respectively). Miconazole was found to be negative for induction of chromosome gaps, breaks, or fragments, or exchange of chromosome pieces.

A dominant lethal test was conducted in male and female mice. After a single oral administration of 40, 160, or 640 mg miconazole/ kg (HED= 3, 13, or 53 mg/kg respectively) to either male or female mice, mated to untreated animals, no induction of a dominant lethal mutation in germ cells was demonstrated.

In studies not previously reviewed, miconazole was negative in an in vitro plate incorporation test and in an in vivo sex-linked recessive lethal test. In the in vitro non-disjunction test in the fungus *A. nidulans*, an increase in the number of abnormal and non-disjunctional colonies observed at cytotoxic dose levels.

Reproductive Toxicology Studies:

A segment I study was performed in rats at doses up to 320 mg/kg/day. No adverse effects were reported on fertility.

Segment II studies were performed in rats and mice with dietary administration, in rats and rabbits by gavage, and in rats and rabbits treated intravenously. No evidence of teratogenicity was reported. In rats receiving doses in the diet of up to 160 mg/100 g food (160 mg miconazole nitrate/kg/day), no embryotoxic effects were reported. In rats receiving 100 mg

miconazole nitrate/kg/day (HED= 16.7 mg/kg) by gavage, increased duration of gestation and decreased number of live pups were reported. The review of NDA 18-520 describes dystocia in rats at "high doses that are associated with other forms of maternal toxicity." In mice fed approximately 80 mg miconazole nitrate/kg/day in the diet (HED=6.7 mg/kg), no maternal toxicity or embryotoxicity were reported. Rabbits receiving 80 mg miconazole nitrate/kg/day (HED = 26.7 mg/kg), an increased number of resorptions and decreased number of live pups were reported. No toxicological effects were reported in studies of intravenous administration of up to 40 mg/kg/day in rats and 20 mg/kg/day in rabbits (HED 6.7 mg/kg/day).

In a segment III study in rats fed doses of miconazole nitrate \geq 80 mg/kg/day, maternal toxicity (decreased body weight gain and decreased food consumption) and embryotoxicity (decreased number of live pups) were seen. At doses of 160 and 320 mg/kg/day in that study, effects seen included increased gestation length, decreased survival rates and decreased body weight at weaning. In rabbits, no maternal toxicity was seen at 80 mg/kg/day (HED = 26.7 mg/kg/day), but there was a significant decrease in the number of surviving pups.

The following studies have not been previously submitted:

1. **Study title:** Vaginal irritation study (10 days) of miconazole 4% cream in rabbits

Study number: DS-5050

Performing organization:

b(4)

Drug lot and batch: lot # 4666-39 SRN 4836, 9 g tube
lot # 4666-39 SRN 4837, 25 g tube

Date of study: report date 5/30/86

GLP compliance: yes

Study design:

Dosing: once daily intravaginal administration for 10 days

Dose groups: Three animals each were treated with 1.0 ml of test material from a 9 g or a 25 g tube that had been stored for 90 days. Six animals served as sham controls; an empty catheter was inserted daily. Three additional animals were untreated controls.

Formulation: not specified, but presumably Monistat 7 cream

Test animals: female New Zealand White rabbits, 3.5-5.0 kg. Animals were observed daily.

Body weights were determined on days 1 and 11. The rabbits were euthanized on day 11. Gross examination was performed of the abdominal and thoracic viscera and vagina and microscopic examination and irritation scoring was performed for the vagina.

Findings:

Deaths: no treatment-related deaths

Clinical signs: No abnormal signs were seen on daily observations. There was no apparent effect on body weight changes.

Pathological examination: On gross examination, there was a slight vascular redness of the vaginal mucosa in all animals except for two of the three untreated controls. On microscopic examination, irritation scores of 8.3 and 5.7 were assigned for the 9 and 25 g tube treated animals, respectively. Irritation scores were 7.7 for sham controls and 3.0 for untreated control animals. Those irritation scores were within the range defined as mild to moderate and were considered acceptable. A "thick creamy material" was present in the vaginas of two rabbits treated with material from the 25 g tube, but was not further characterized.

2. Voogd CE and vander Stel JJ. Are econazole, miconazole and clotrimazole mutagenic to bacteria? *Mutation Research* 120:91-95, 1983.

A "fluctuation test" was performed in *Klebsiella pneumoniae* ur⁺pro⁻ and *E. coli* K12 Hfr at miconazole concentrations of 200 and 300 mg/L. A plate incorporation test with and without metabolic activation (S9) was performed in *Salmonella typhimurium* strains TA98 and TA100 at miconazole concentrations up to 200 mg/L. No mutagenic effects were observed in either of these tests. *Reviewer's comment: The maximum concentration for in vitro genotoxicity tests is defined by the ICH to be 5 mg/mL, or approximately 20 times the highest concentration used in these studies.*

3. **Study title:** Toxicological studies on miconazole (report 8): Mutagenicity tests of miconazole. (translated from Japanese)

Study number: not specified

Performing organization:

b(4)

Drug lot and batch: not stated

Date of study: January to April, 1976

GLP compliance: not stated

Study design and results:

A sex-linked recessive lethal mutagenicity test was performed in *Drosophila melanogaster*. The rate of the lethal mutation was 0.3 and 0.7% for 0.5 and 0.1 M treatment groups compared to 0.4% for the control group. The positive control, ethyl methanesulfonate induced the mutation at a rate of 42.9%.

The dominant lethal test was performed in mice. A single oral dose of 650 mg miconazole/kg (1/4 the oral LD₅₀) was administered. A slight increase in the rate of appearance of the dominant lethal mutation was seen in the fourth and fifth weeks relative to control, but the increases were far less than those seen in the group treated with the positive control, cyclophosphamide. The test was judged to be negative.

Cytogenetic studies in mice were conducted at single doses of 650 mg miconazole/kg po or 170 mg miconazole/kg ip (1/4 of the respective LD₅₀'s). At 4 and 22 hours after dosing, 10 mg/kg colchicine was administered, followed by sacrifice at 6 or 24 hours, respectively. Bone marrow was evaluated for chromosomal abnormalities. The positive control was ethyl methanesulfonate. The study was negative; there was no significant difference for abnormalities seen in miconazole-treated animals vs. controls.

4. Bellincampi D. et al. Membrane-damaging agents cause mitotic non-disjunction in *Aspergillus nidulans*. *Mutation research* 79:169-172, 1980.

Miconazole was tested at 0.41 and 4.16 µg/mL. At the high concentration, a significant increase in non-disjunctive colonies was observed (this concentration also decreased the fungal survival rate). Although the mechanism is unclear, miconazole is known to cause membrane damage. The authors speculate that disruption of normal mitosis could be one of the major actions of this class of drug on fungi. The authors hypothesize that the same effect could occur

in eukaryotic organisms as well due to evidence in plants and animals that there are connections between the mitotic apparatus and the nuclear membrane.

NONCLINICAL PHARMACOKINETICS STUDIES

No new nonclinical ADME studies were performed with the to-be-marketed formulation. Absorption of miconazole is reported to be low after topical or intravaginal application (The applicant does not differentiate between miconazole or miconazole nitrate here). Radiolabel studies were performed to assess pharmacokinetics.

Absorption of 4 mg/kg ^3H -miconazole nitrate in a 2% ointment was evaluated after topical application to depilated sites on female Wistar rats. After a single 8-hour exposure, C_{max} was 0.08 μg -equivalents/g at 8 hours; plasma concentrations then declined to near baseline (0.01 μg -equivalents/g) by 48 hours. When 20 mg/kg ^3H -miconazole was administered by the intravaginal route to rats (pregnant and nonpregnant), C_{max} was 0.04 μg -equivalents/g at 6 hours, followed by a rapid decline in plasma concentrations to near baseline (0.01 μg -equivalents/g) by 48 hours. Intravaginal administration of 20 mg/kg ^3H -miconazole nitrate to rabbits resulted in maximal plasma concentrations of 8.57 and 9.66 μg -equivalents/mL at 3 and 8 hours after dosing, respectively. When ^3H -miconazole nitrate was administered intravenously to rats at a dose of 1 mg/kg in 10% PEG 400, a biphasic decline was observed, and the rate of decline was slightly greater in male rats. By 24 hours, plasma concentrations were down to 0.05 and 0.02 μg -equivalents/g for females and males, respectively. Intravenous administration of 1 mg/kg ^3H -miconazole in 10% PEG solution to rabbits or dogs yielded results similar to those found in the rat. Oral administration to rats of 10 mg/kg ^3H -miconazole in a 0.5% aqueous solution of carboxymethyl cellulose resulted in C_{max} at 1 hour of 1.41 μg -equivalents/mL. Plasma concentrations were down to 0.13 μg -equivalents/mL by 72 hours. In another study, 1-30 mg/kg (aqueous) ^{14}C -miconazole was administered orally to rats. Dose-related absorption was observed, with C_{max} at 1 hour of 0.59 μg -equivalents/g after a 3 mg/kg dose and 4.13 μg -equivalents/g after a 30 mg/kg dose. Elimination kinetics were biphasic, with half lives similar to intravenous administration, but the half life was again longer in females than in males. In non-fasted rats, absorption was delayed and concentrations were lower than in fasted animals.

The pattern of tissue distribution of radiolabeled miconazole nitrate was similar with all routes of administration, however, tissue concentrations after topical administration were at least 20-fold lower than after oral administration. After oral administration of ^{14}C -miconazole nitrate to Wistar rats at 1, 3, 10, or 30 mg/kg, maximal concentrations of radioactivity were seen in the liver, small intestine, stomach, adrenals, and lungs at 1-3 hours. After three hours, concentrations decreased at a rate similar to or greater than in plasma. At the highest dose, high levels were present in tissues for 1-6 hours. By 168 hours, the radiolabel was not detectable in any tissue except liver. Tissue levels were higher in females than in males.

After topical administration of 4mg/kg ^3H -miconazole nitrate ointment to rats, the highest radioactivity was seen in liver, kidney, lung, adrenal, and thyroid at 24 hours (0.67, 0.41, 0.28, 0.2, 0.12 μg -equivalents/mL, respectively). Less than 0.1 μg -equivalent/g was found in heart spleen, thymus, pituitary, brain, uterus and ovaries. After intravaginal administration, the findings were similar except for higher concentrations in the uterus.

After intravenous administration, the tissue rank order was similar to that after topical and oral dosing, but concentrations were initially high in the adrenals. At 72 hours, liver contained

<0.05 µg-equivalents/mL; the applicant cited this finding as evidence of little potential for tissue accumulation (*Reviewer's comment: That assumption is not necessarily true in the event that absorption is slow and thus governs the rate of elimination.*).

Whole body autoradiography was performed in the rat after oral administration of 10 mg/kg ³H-miconazole nitrate. At one hour, high levels of radioactivity were present in the liver, gastric contents and digestive tract. Lower levels were seen in kidneys>adrenals>brown fat, and comparable levels were seen in heart, lungs, Harderian glands and submandibular glands. After six hours, high levels were present in the lower gastrointestinal tract, and there was a moderate decrease in liver and gastric content radioactivity. At 24 hours, small amounts of radioactivity were present in liver, and at 168 hours, virtually no radioactivity was observed. Tissue levels of radioactivity were higher in females than in males, with high levels in the adrenals and ovaries. In pregnant females, radioactivity was seen in the placenta and fetuses at one hour; concentrations in those tissues were higher than in blood. Levels decreased with time, and were essentially gone by 24 hours.

Plasma protein binding in human serum was 90-93% at concentrations between 10-100 mg/ml. Binding was primarily to albumin.

The applicant states that miconazole is highly metabolized in humans and animals. After oral administration to rats, no unchanged drug is excreted in the urine, and 22-28% of the oral dose is excreted in feces unchanged. Miconazole undergoes O-dealkylation to form 2,4-dichlorophenyl-1-imidazole ethanol (excreted in feces, accounts for 10% of administered dose, <1% in urine), which is oxidized and N-dealkylated to form 2,4-dichloromandelic acid (excreted in urine and feces, accounting for 9.6% and 18%, respectively, of the administered dose). After oral administration in the rat, the parent compound also undergoes oxidative N-dealkylation to form a metabolite which has lost the imidazole ring and is excreted in the urine (7.3%) and feces (10.1%). There are also small amounts of other metabolites <5%.

Twenty-four hours after topical administration of 4 mg/kg to female rats, approximately 16% of the radioactive dose was excreted in feces and 2% was excreted in urine. An additional 10% was excreted in feces in the next 24 hours. After 7 days, 29% of the dose was excreted cumulatively in the feces and 3% in urine. Elimination in the feces is also the major route after oral or intravenous dosing. By 24 hours after an oral dose, almost 90% was eliminated (14% from urine and 75% from feces). Another 5% was excreted in feces after one week. Females exhibited slightly lower urinary excretion than males, with a total of 85% of the dose excreted in 24 hours and 97% in 168 hours. Similar results were seen after intravenous dosing. Fecal excretion accounted for more than 75% of elimination in all species tested, and was mostly by the biliary route. Twenty-four hours after an intravenous dose to bile duct-cannulated rats, 68% of the dose had been excreted into the bile. Enterohepatic recirculation was demonstrated.

After intravenous administration of 1 mg/kg ³H-miconazole nitrate to female rabbits, excretion was slower than in the rat: 52% was eliminated by 24 hours, and 73% was eliminated by 48 hours (27% in urine and 47% in feces). After seven days, 88% of the total dose had been excreted. After intravenous administration of the same dose to female dogs, 77% of the total dose was excreted over seven days (7.4% in urine, 69% in feces).

NONCLINICAL PHARMACOLOGY STUDIES

Nonclinical pharmacology studies have been submitted and reviewed previously.

Neuropharmacological studies were performed in white mice and Wistar rats at oral doses of 2% miconazole nitrate (40 mg/kg). No significant changes relative to control were noted in any of the studies. Parameters examined were pupil diameter, licking reflex time after being dropped on a hot plate, and general behavior in mice. Parasympathomimetic activity, parasympatholytic activity, CNS stimulation, body temperature, morphine-like properties, and anticonvulsant effects were evaluated after a single administration in male rats. In female rats administered daily doses in food for seven days, food consumption, body weight, fecal and urine output, pupil diameter, body temperature, O₂ consumption, biochemical profiles, thymus and adrenal weights were not different from controls.

Cardiovascular studies were performed in dogs, monkeys, and cats. In the dog, after an intravenous dose of 2.5 mg/kg of 2% miconazole nitrate, a slight increase in blood pressure effect after epinephrine administration was seen in repeated studies. No effect was seen on resting blood pressure. It was determined later that PEG in the vehicle was most likely responsible for the blood pressure response. In dogs administered intravenous doses of 4-29 mg/kg of 2% miconazole nitrate, increased Q-T interval was seen as well as frequently induced ventricular fibrillation after epinephrine challenge. Monkeys were administered oral doses of 2% miconazole nitrate up to 100 mg/kg. An increase in Q-T interval was seen in all animals, but ventricular fibrillation was not induced after epinephrine challenge. Cats were administered intravenous doses of 5 mg/kg (what salt and percent) every 25 minutes for a cumulative dose of 20 mg/kg. Ventricular fibrillation following epinephrine challenge was not seen.

In vitro studies were performed to evaluate 2% miconazole nitrate using gastrointestinal tissue from rats, guinea pigs, and rabbits. There was no apparent adrenergic effect at alpha receptor sites (in rabbit spleen). No effect was seen on baseline contractility of guinea pig ileum, rabbit spleen, or rat stomach was seen at concentrations up to 10 mg/L. There was no inhibition of serotonin activity on rat stomach fundus at concentrations up to 10 mg/L. In guinea pig ileum, concentrations up to 10 mg/L antagonized the spasmogenic effect of all spasmogens tested, including bradykinin, serotonin, nicotine, eledoisin, angiotensin, and histamine. In rabbit duodenum, there was a slight increase of initial tonus at 2.5-10 mg/L, spontaneous movement was enhanced at 2.5 mg/L, but no anticholinergic activity was demonstrated. Irreversible depression of the dose-response curve for histamine was demonstrated in guinea pig ileum. This effect was determined to be non-competitive antagonism of histamine. Also in guinea pig ileum, a marked but slow antagonism to methacholine, bradykinin, histamine, and angiotensin at concentrations as low as 0.16 mg/L was demonstrated. In fowl rectal cecum, concentrations of up to 10 mg/L did not inhibit isoproterenol activity. No adrenergic blocking activity was observed at beta-receptor sites.

The effect of 2% miconazole nitrate on cat papillary muscle in vitro was examined. A weak negative inotropic effect was induced by the highest concentration, 10 mg/L.

PREVIOUS HUMAN EXPERIENCE

In a pharmacokinetics study involving seven days of application at each diaper change, drug levels were measurable in 3/18 infants (approximately 20% of subjects) treated with multiple daily doses of 0.25% miconazole nitrate ointment. Serum levels were between 3.0-3.8 ng/mL (LOD=1 ng/ml) in those subjects.

The applicant reports that there is little potential for dermal toxicity or irritation with this product. Out of 252 infants treated with 0.25% miconazole nitrate ointment, the applicant reports that there was only one drug-related adverse event. The applicant also reports that in post-marketing surveillance for the OTC product marketed abroad there were two possibly drug-related adverse events.

The applicant estimates that diaper dermatitis should be limited to about eight episodes during the first two to three years of life, with an average duration of three days per episode. They state that even though a severe episode could take as much as ten days to resolve, use of the drug product would not be chronic. This estimate does not take into account exposures to the drug substance later in life for treatment of dermatophytoses, etc.

The drug product is marketed for this indication in several European countries. It was disapproved in Norway because of concerns related to topical absorption in infants and development of resistant organisms.

SUMMARY

Studies of a 0.25% miconazole nitrate ointment that is nearly identical to the proposed drug product include acute oral toxicology in the mouse and rat, acute dermal toxicology in rabbits, and dermal and ocular irritation studies in rabbits. No mortality was seen in acute oral studies at doses in mice and rats equivalent to human doses of 8.3 and 6.25 mg/kg, respectively. Observations included slight decreases in activity, body tone and righting reflex and slight diarrhea. In the acute dermal toxicity study, effects were limited to edema at the treatment site after 24 hour occlusion of a dose equivalent to 1.7 mg/kg in humans. Miconazole nitrate ointment was a mild to moderate skin irritant and was not an ocular irritant in irritation studies.

Oral and intravenous studies of miconazole in rats, rabbits, and beagle dogs have demonstrated that the liver is the target organ of toxicity. NOEL's were 5.5 mg/kg/day po in rats for 78 weeks (HED = 0.92 mg/kg/day, or 0.2 times the maximum clinical daily dose), 5 mg/kg/day iv in rabbits for 6 months (HED = 1.7 mg/kg/day, or 0.4 times the maximum clinical daily dose), and 5 mg/kg/day po in dogs for 52 weeks (HED = 2.5 mg/kg, or 0.55 times the maximum clinical daily dose). A six-month dermal toxicology study in rabbits revealed local effects at the treatment site only. The NOEL for that study was 40 mg/kg/day (HED = 13 mg/kg/day, or three times the maximum clinical daily dose).

Miconazole was negative for genotoxicity in most studies, although the concentrations used may not have been adequately high. Miconazole was positive for genotoxicity in the non-disjunction test in *Aspergillus nidulans*.

In reproductive and developmental toxicology testing, miconazole did not appear to have effects on fertility or teratogenicity. In the rat, at doses equivalent to 16.7 mg/kg in the human, the duration of gestation was increased and the number of live pups was decreased. In the rabbit, at doses equivalent to human doses of 26.7 mg/kg, resorptions were increased and the number of live pups was decreased. Segment 3 studies in rats and rabbits demonstrated decreases in pup body weights and decreased pup survival.

ADME studies demonstrated low absorption of miconazole after dermal application. Drug distribution was primarily to liver, kidney, lung, adrenal, and thyroid after topical administration. In vitro, miconazole was >90% bound to plasma proteins (primarily albumin) in human blood. Miconazole is highly metabolized in man and animals. It is excreted primarily in the bile, with enterohepatic recirculation. Smaller amounts of metabolites are excreted in urine.

Safety pharmacology studies were conducted to investigate effects on the nervous system, cardiovascular system, and digestive system. Findings in neuropharmacology studies were unremarkable. In cardiovascular studies in multiple species, the Q-T interval of the ECG was prolonged, and increased sensitivity to induction of ventricular fibrillation after epinephrine challenge was noted. In studies of effects on the gastrointestinal tract, antagonism of spasmogens was noted, as was non-competitive antagonism of histamine. Neither anticholinergic activity nor β -adrenergic blockade were observed.

COMMENTS

Systemic exposures in rats at oral doses similar to those producing liver toxicity were approximately 4 $\mu\text{g}/\text{mL}$ in plasma. At a dose near the NOEL in the oral study in rats, C_{max} was 0.6 $\mu\text{g}/\text{ml}$. In some infants in clinical trials, plasma levels were measurable and were 3-4 ng/ml . This would seem to indicate a relative margin of safety of two orders of magnitude in patients under conditions of short-term treatment.

CONCLUSIONS

From a nonclinical standpoint, the application is approvable, with the following label revisions.

RECOMMENDATIONS

The following recommendations are made for the the label:

1. Under **CLINICAL PHARMACOLOGY**, the review team may wish to consider mention of hepatic metabolism of miconazole in man and animals.
2. Under **PRECAUTIONS**,
 - a. The Belgian label warns against use of the product on open wounds. The review team may wish to consider a similar statement.
 - b. The following section should be added:

Carcinogenesis, mutagenesis, impairment of fertility: Studies to evaluate the carcinogenic potential of Pediastat in animals have not been performed.

Miconazole was negative in a test for gene mutation in *Salmonella typhimurium* strains TA100 and TA98. Miconazole was also negative in micronucleus assays in mice and rats administered up to a human equivalent dose of 53 mg/kg orally or intraperitoneally, respectively. Miconazole was negative in a chromosome aberration test in mice and in a dominant lethal test in male and female mice. Evaluation of miconazole in an in vitro plate incorporation test and in an in vivo sex-linked recessive lethal test also yielded negative results. In an in vitro non-disjunction test in the fungus *A. nidulans*, an increase in the number of abnormal and non-disjunctional colonies was observed at cytotoxic dose levels. The relevance of the latter test to mammals is unknown.

Miconazole had no adverse effect on fertility in a study in rats at oral doses up 100 times the human topical exposure, assuming 10% bioavailability of the topical product.

d. The **Pregnancy/Nursing Mothers** section should be modified, since the drug will be administered by caregivers who may be pregnant or nursing and could be exposed to the drug, as follows:

Pregnancy: Pregnancy Category C. Miconazole nitrate administration has been shown to result in prolonged gestation and decreased numbers of live young in rats, and increased number of resorptions and decreased number of live young in rabbits at oral doses 33 and 53 times the human topical exposure, respectively, assuming 10% bioavailability. There are no adequate and well-controlled studies of Pediastat in pregnant women. Pediastat should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known if Pediastat may be present in milk. Appropriate precautions should be followed when administering the product.

e. Under **OVERDOSAGE**, information should be added to describe acute oral toxicity studies, to identify the liver as the target organ of toxicity, and to describe possible increased sensitivity to catecholeamines seen in animal cardiovascular pharmacology studies.


Amy C. Nostrandt, D.V.M., Ph.D.
Pharmacologist/Toxicologist

cc:

NDA 21-026

HFD-340

HFD-540

HFD-540/PHARM/Nostrandt

HFD-540/TLPHARM/Jacobs

HFD-540/MO/Ko

HFD-540/CHEM/Timmer

HFD-540/PMS/Wright

C:\word files\nda\n21026_000.doc

Concurrence Only:

HFD-540/DD/WILKIN  5/23/99

HFD-540/TLPHARM/JACOBS 0.9 5/15/99

Appears This Way
On Original

The formula used in acute oral and dermal studies and in dermal and ocular irritation studies is identical to the to-be-marketed formulation with the exception of the fragrance component. Other studies were performed using Monistat™ cream to support approval of that product in a previous NDA.

- (6) Are the proposed labeling sections relative to pharm/tox appropriate (including human dose multiples expressed in either mg/m² or comparative serum/plasma levels) and in accordance with 201.57?
Comments?

No nonclinical studies are discussed in the proposed label. Addition of such information may be recommended at a later date, depending on the outcome of the review.

- (7) Has the Sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor?
Comments?

No special studies were requested beyond those already conducted.

- (8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the Sponsor submitted a rationale to justify the alternative route?
Comments?

The sponsor has conducted both systemic and topical studies.

- (9) Has the Sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?
Comments?

- (10) Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics?
Comments? Not applicable

- (11) Has the Sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?
Comments?

- (12) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not.

(13) If the NDA is fileable, are there any issues that need to be conveyed to Sponsor? If so, specify: _____ X

(14) Issues that should not be conveyed to the Sponsor:

Cathy C. Nostand 10/11/98
Reviewing Pharmacology Officer

Adey J. Lurie 10/12/98
Pharmacology Team Leader

**Appears This Way
On Original**