PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

MONISTAT* Derm Cream

miconazole nitrate
vaginal cream 2%

Antifungal Agent

Insight Pharmaceuticals LLC
660 White Plains Road, Suite 250
Tarrytown, NY 10591, USA

Date of Initial Approval:
December 31, 1980

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Submission Control No: 242581
*Trademark

RECENT MAJOR LABEL CHANGES

None.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MONISTAT* Derm Cream is indicated for:

- the topical treatment of dermatophytes and Candida infections
- the lesions caused by mixed infections involving susceptible fungi
- used clinically in conjunction with vaginal ovules or suppositories in MONISTAT*3 and 7 DUAL-PAKS, respectively when symptoms of vulvovaginal candidiasis are particularly extensive.

1.1 Pediatrics

Pediatrics (ages 12 and under): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

MONISTAT* Derm Cream is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Should not be used for self-medication if vaginal pruritus or discomfort is occurring for the first time (see Warnings - General section below);
- Should not be used for self-medication if fever, nausea, unexplained pain in the lower back, lower abdomen, or either shoulder, or foul-smelling vaginal discharge are present (see Warnings - General section below);
- Discontinue use if sensitization or other signs of irritation not present before therapy occur (see Warnings - General section below);
- Intractable candidiasis may be the presenting symptom of unrecognized diabetes. If unresponsive to therapy appropriate microbiological studies should be repeated to confirm the diagnosis of vulvovaginal candidiasis (see Warnings - Endocrine section below);
- Should not be used by pregnant or nursing women without consulting health professional (see Warnings - Pregnant Women section below);
- Refrain from intercourse during therapy (see Warnings - Sexual Health section below);
- Therapy reduces the effectiveness of latex condoms and diaphragms (see Warnings - Sexual Health section below);
- Should not be introduced into the eyes (see Warnings - General section below);
- Anticoagulant effect (see Warnings - General section below).

4.2 Recommended Dose and Dosage Adjustment

Apply sufficient MONISTAT* Derm Cream to cover the affected area twice daily, morning and evening. Massage gently until cream disappears.

Early clinical improvement (1-2 weeks) has been seen in treatment of infections caused by dermatophytes and Candida species and in mixed fungal infections, but resistant lesions may take longer to clear. Candida infections should be treated for two weeks and dermatophyte infections for one month in order to reduce the possibility of recurrence. If a patient shows no clinical improvement after 30 days of treatment, the diagnosis should be reconsidered.

Health Canada has not authorized an indication for pediatric use. Please see Pediatrics Section.

4.3 Administration

Apply sufficient MONISTAT* Derm Cream to cover the affected area twice daily, morning and evening. Massage gently until cream disappears.

4.4 Reconstitution

Not applicable.

4.5 Missed Dose

Not applicable.

5 OVERDOSAGE

Although highly unlikely to occur, in the event of a substantial overdose, and if taken concomitantly with other drugs (e.g. coumarin derivatives, oral hypoglycaemics or phenytoin), the effects and side effects of the other drugs can be increased.

MONISTAT* Derm Cream is intended for local application and not for oral use. In the event of accidental ingestion of large quantities of MONISTAT* Derm Cream, contact a doctor or Poison Control Centre at once. Keep this and all other medications out of the reach of children and pets.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	Cream 2% Water miscible, white cream containing 2% miconazole nitrate as the active ingredient	Benzoic Acid, Cetyl Alcohol, Isopropyl Myristate, Polysorbate 60, Potassium Hydroxide, Propylene Glycol, Stearyl Alcohol, Water

The cream is packaged in a 15-gram or 30-gram laminate tube. The tube is packaged in a paperboard carton.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

Discontinue medication if sensitization or marked irritation (rash, burning, blistering, redness) not present before therapy occur.

Avoid introducing MONISTAT* Derm Cream into the eyes.

Patients should not use MONISTAT* Derm Cream for self-medication if vaginal pruritus or discomfort is occurring for the first time. In this instance, a physician must be consulted to establish the diagnosis of vulvovaginal candidiasis.

Patients should not use MONISTAT* Derm Cream for self-medication if fever, nausea, unexplained pain in the lower back, lower abdomen, or either shoulder, or foul-smelling vaginal discharge are present, as a condition more serious than vulvovaginal candidiasis may exist.

Patients should be advised to discontinue medication if sensitization or other signs of irritation (skin rash or hives, burning, blistering, redness) not present before therapy occur.

Miconazole administered systemically is known to inhibit CYP3A4/2C9. Due to the limited systemic availability after vaginal application, clinically relevant interactions occur very rarely. Patients taking prescription blood thinners, such as warfarin, should talk to their physician or pharmacist before using MONISTAT* Derm Cream due to the risk of bleeding and bruising. Caution should be exercised and the anticoagulant effect should be monitored.

Endocrine and Metabolism

Intractable candidiasis may be the presenting symptom of unrecognized diabetes; thus appropriate urine/blood studies may be indicated in patients not responding to treatment. In any case, if a patient is unresponsive to therapy appropriate microbiological studies should be repeated to confirm the diagnosis of vulvovaginal candidiasis and to rule out other pathogens.

Sexual Health

Reproduction

Miconazole nitrate preparations reduce the effectiveness of latex condoms and diaphragms. With MONISTAT* Derm Cream, the use of diaphragms and condoms is not recommended during therapy and for 3 days afterwards. Condoms and diaphragms may be damaged and fail to prevent pregnancy or sexually transmitted diseases.

Function

During therapy, instruct the patient to refrain from intercourse.

7.1 Special Populations

7.1.1 Pregnant Women

Pregnant patients should be advised either to exercise caution in the use of the vaginal applicator for the ovule or to insert the ovule digitally.

Follow-up reports on infants born to twenty-six pregnant patients who participated in European and North American clinical evaluations of Miconazole Nitrate 100 mg Suppositories and infants born to 167 of 263 pregnant patients (some follow-up reports are not yet available) who participated in North American clinical evaluations of Miconazole Nitrate 2% Cream administered in a 14-day regimen described no complications or adverse effects attributed to

this therapeutic agent. Nevertheless, since miconazole nitrate is absorbed in small amounts from the human vagina, MONISTAT* vaginal preparations should not be used by pregnant or nursing women unless the physician considers it essential to the welfare of the patient

7.1.2 Breast-feeding

It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk precaution should be exercised.

7.1.3 Pediatrics

Pediatrics (ages 12 and under): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. Please see Pediatrics Section.

7.1.4 Geriatrics

Not applicable. Please see Geriatrics Section.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

On rare occasions it has been reported that patients treated with MONISAT* Derm Cream experienced mild pruritus, irritation and burning at the site of application

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates. None.

8.3 Less Common Clinical Trial Adverse Reactions

Not applicable.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Not applicable.

8.5 Clinical Trial Adverse Reactions (Pediatrics)

Not applicable. Please see Pediatrics Section.

8.6 Post-Market Adverse Reactions

None.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions Box

Serious Drug Interactions

- Patients taking prescription blood thinners should talk to their physician or pharmacist before using MONISTAT* due to the risk of bleeding and bruising.

9.2 Overview

Patients taking prescription blood thinners, such as warfarin, should talk to their physician or pharmacist before using MONISTAT* due to the risk of bleeding and bruising. Caution should be exercised and the anticoagulant effect should be monitored.

9.3 Drug-Drug Interactions

Not applicable.

9.4 Drug-Food Interactions

Not applicable.

9.5 Drug-Herb Interactions

Not applicable.

9.6 Drug-Laboratory Test Interactions

Not applicable.

9.7 Drug-Lifestyle Interactions

Not applicable.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Depending upon concentration, miconazole nitrate exhibits broad spectrum in vitro fungistatic or fungicidal activity against species of the genus Candida. Miconazole nitrate also inhibits several other genera of fungi, including dermatophytes and yeasts, as well as gram positive bacteria.

Miconazole nitrate inhibits the biosynthesis of ergosterol or other sterols, damaging the fungal cell wall membrane and altering its permeability. In fungi, it also inhibits biosynthesis of

triglycerides and phospholipids as well as oxidative and peroxidative enzymes. The latter action results in intracellular buildup of toxic concentrations of hydrogen peroxide, which may contribute to deterioration of subcellular organelles and cellular necrosis.

Candida albicans cells have been observed to exhibit progressive cytoplasmic deterioration and prominent shape changes resulting in complete cell necrosis depending on the dose and duration of exposure to miconazole nitrate. The sequence of morphologic alterations induced by miconazole nitrate at fungistatic doses (10^{-6}M) are lysis of cytoplasmic organelles, focal to complete loss of cell plasmalemma and irregular thickening of the cell wall containing multiple inclusions. Administration of fungicidal doses (10^{-4}M) induces a completely necrotic cell interior with an unaltered cell wall.

Miconazole nitrate has been clinically effective in treating tinea pedis (athlete's foot), tinea cruris, tinea corporis, and tinea versicolor caused by dermatophytes. MONISTAT* Derm Cream is also effective in cutaneous candidiasis. Among the organisms against which MONISTAT* Derm Cream has been found effective are Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton interdigitale, Epidermophyton floccosum, Micosporum canis, Micosporum gypseum, species of Candida including C. albicans, and Maleassezia furfur.

Not all species or strains of a particular organism may be susceptible to miconazole nitrate.

To date, no wild strains or fungal mutants with substantial acquired resistance to miconazole have been reported; however, miconazole resistant Candida albicans has been isolated from an infant following bladder irrigation with miconazole for the treatment of urinary candidiasis.

10.2 Pharmacodynamics

ANIMAL
Tissue and Whole Animal
The agonist of miconazole on the guinea pig ileum, rabbit duodenum, rabbit spleen and rat stomach fundus tissue preparations is limited to a slight initial tonus increase observed with the rabbit duodenum preparation at concentrations of 2.5 – 10 mg/l. this compound is observed to antagonize the spasmogenic effects of bradykinin, serotonin, nicotine, eledoisin, angiotensin and histamine, but is devoid of anticholinergic (rabbit duodenum), antiserotoninergic (rat stomach fundus) anti-"-adrenergic rabbit spleen) and ß-adrenergic blocking (fowl rectal caecum) activity.

Miconazole given to mice in a single dose of 40mg/kg had no influence on the licking reflex or other gross behavioural characteristics. In addition, rats treated with this regimen showed no autonomic or CNS induced effects. As well, no morphine-like properties, anticonvulsant effects or change in body temperature was recorded in this species. After repeated administration at this dose level (40 mg/kg/day for 7 consecutive days) no significant changes were again observed in behavioural characteristics and gross overall condition of pathological examination at autopsy.

10.3 Pharmacokinetics

Absorption:

HUMAN
The absorption, metabolism and excretion of orally, intravaginally and topically administered

labelled miconazole nitrate were observed in healthy normals. Blood, urine and faecal samples were taken. The study indicated that the absorption and excretion of miconazole administered orally were unrelated to dosage and duration of treatment.

Although 10-20% of the administered oral dose of radioactivity could be recovered in the urine, less than 1% was due to unchanged miconazole nitrate. A large amount of the 40- 55% of administered dose recovered in the feces was unchanged miconazole nitrate. Only about 1% of the administered intravaginal dose of radioactivity was recovered from urine and only 0.14% to 0.67% of the topically administered dose, indicating low absorption from each. Eight hours after topical examination, 90% of the drug was recovered from the skin.

Topical administration of MONISTAT* miconazole nitrate cream 2% has been effective in the local treatment of fungal infections of the skin and nails, including tinea pedis, tinea cruris, tinea corporis, as well as tinea versicolor. Clinical studies have involved several treatment periods but experience indicates that topical applications should continue for two weeks for tinea cruris, tinea corporis and tinea versicolor and for four weeks for tinea pedis, to lessen the probability of recurrence.

Intravaginal administration of MONISTAT* miconazole nitrate 2% for 7 days has been determined to be effective for the treatment of vulvovaginal candidiasis. Clinical experience has indicated that the administration of a small amount of MONISTAT* Derm miconazole nitrate 2% cream to the vulvar area when an intravaginal solid dosage form such as MONISTAT* 7 Vaginal Suppositories or MONISTAT* 3 Vaginal Ovules are being used provides the added benefit of the cream form for particularly severe external symptoms of itching and irritation.

Distribution: Not applicable.

Metabolism:

a) In Vitro

Rats (miconazole nitrate tritium labelled on the 2-ethyl group)
Incubation of tritium-labelled miconazole nitrate was carried out with the 10,000 gm supernatant fractions and microsomal fractions of the liver, lungs and kidneys of the Wistar rat. The major metabolite was "-(2,4-dichloro-phenyl)-1H-imidazole-1-ethanol (R 14821). Whereas more than 70% of the drug was unmetabolized, this metabolite, resulting from an oxidative O - dealkylation by microsomal enzymes, amounted to about 20% of total reactivity. The microsomal enzymes responsible for this metabolic breakdown were twice as active in the liver as in the lungs or the kidneys.

Humans (miconazole nitrate tritium labelled on the 2-ethyl group
The binding of miconazole nitrate to human plasma proteins, and the distribution of the drug in human blood, blood cell suspension and ghost cell suspension were studied by equilibrium dialysis. Human blood was obtained by venous puncture from health male (8) and female (3) volunteers who had not taken any medication for at least two weeks, from patients (4) with chronic renal failure and from patients (4) who were under haemodialysis treatment.

Miconazole nitrate was found to bind very strongly to human plasma proteins. For example, a 4% HSA solution bound miconazole nitrate for 98% with an overall association constant of 91.6×10^3. Even a 1.5% human gamma globulin solution bound the drug for about 81% with

an overall association constant of 8.0 x 10^3. The binding of miconazole nitrate to the plasma proteins amounted to 98.7%. In blood, 1.2% was distributed in the plasma water, 88.2% was bound to the plasma proteins and 10.6% to the blood cells.

The percentage of bound miconazole was not influenced by the total drug concentration within the tested range from 0.1 to 10.0 x 10^{-6}M. In a blood cell suspension 97.6% of the drug was bound to the blood cells, probably due to the binding properties of not only the cell membranes but also inner constituents such as haemoglobin.

No significant sex differences and only minor individual differences were found for the plasma protein binding and the distribution of miconazole nitrate in blood. Only very small differences were found between the plasma protein binding and the distribution of the drug in blood or normal subjects, of patients with chronic renal failure and of patients under haemodialysis treatment.

b) In Vivo

Studies were conducted using miconazole labelled with titrium at C-2 of the imidazole ring or the ß-carbon of the ethyl side chain. It was noted that the tritium label at C-2 of the imidazole ring was labile.

Rats (miconazole nitrate tritium labelled on the 2-ethyl group)
Five male Wistar rats were each given an oral dose of 40 mg/kg miconazole in PEG-200. During the four days when urine and faeces were collected, 66% of the total radioactivity administered was recovered; 62% after 48 hours. In the urine collected more than 37% of the radioactivity recovered was in the form of tritiated water. At autopsy (day 4) blood, liver and brain tissues contained 1.9% of the administered radioactivity. Examination of the excreta by the inverse isotope dilution method revealed that 18% of the administered dose was excreted unchanged, 19%, as "-(2,4-dichlorophenyl)-imidazole-1-ethanol or its parent ketone and traces as imidazole.

Dogs and Rabbits (miconazole tritium labelled at C-2 of the imidazole ring)
In separate excretion and absorption studies involving 2 animals per study, miconazole was administered intravaginally in carbowax 1000 and wecobee FS and M (7:3) vehicles to beagle bitches (1 mL of 1% formulation) and New Zealand white rabbit doe (0.5 mL of 1% formulation). In the excretion studies urine and faeces were collected for 12 days from the dogs and urine only from the rabbits. In both species the major percentage of the recovered radioactivity was obtained during the 3 days after dosing. In dogs greater than 60% of the radioactivity was in the urine where the carbowax vehicle was used whereas less than 50% was recovered in the urine of dogs given miconazole in the wecobee vehicle. This observation was made with rabbits as well. In the absorption studies blood samples were obtained at 2, 4, 7 and 25 hours. Peak levels in dogs occurred 4 - 7 hours after dosing whereas in rabbits blood levels peaked at 2 hours. The highest level in dogs (0.06 mg/mL) was found with the carbowax vehicle as was the case with rabbits (0.17 - 0.18 mg/mL). At autopsy (25 hours) the vaginas were dissected and washed. Only 0.08% of the administered dose to dogs and 0.456% to rabbits was found in the tissues and washings.

Rabbits (miconazole tritium labelled in the b-carbon of the ethyl side chain)
Vaginal suppositories (2% miconazole) were administered to 2 New Zealand White rabbits. Urine and faeces were collected daily and blood at 3, 6, 24, 72, 96, 144, and 168 hours. Most of the administered radioactivity (90% in one animal and 70% in the other) was

excreted in eight days. Fifty percent of the tritium excreted was recovered in 2-3 days and found in the faeces. Maximum blood levels of tritium occurred 6 hours after dosing (0.95 mg/mL).

Elimination:

HUMAN
The absorption, metabolism and excretion of orally, intravaginally and topically administered labelled miconazole nitrate were observed in healthy normals. Blood, urine and faecal samples were taken. The study indicated that the absorption and excretion of miconazole administered orally were unrelated to dosage and duration of treatment.

Although 10-20% of the administered oral dose of radioactivity could be recovered in the urine, less than 1% was due to unchanged miconazole nitrate. A large amount of the 40- 55% of administered dose recovered in the feces was unchanged miconazole nitrate. Only about 1% of the administered intravaginal dose of radioactivity was recovered from urine and only 0.14% to 0.67% of the topically administered dose, indicating low absorption from each. Eight hours after topical examination, 90% of the drug was recovered from the skin.

11 STORAGE, STABILITY AND DISPOSAL

Monistat* Derm Cream should be stored at controlled room temperature (15 °C - 30 °C).

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

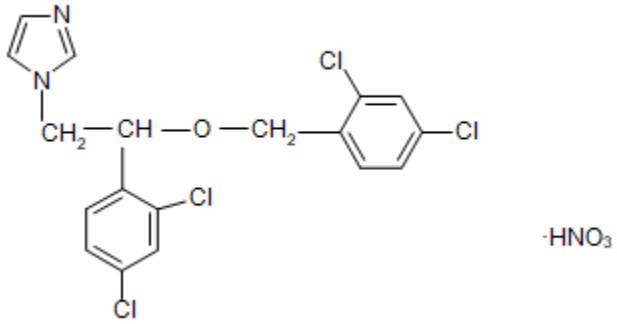
Drug Substance

Proper name: Miconazole Nitrate

Chemical name: 1-{2,4-dichloro-ß-[(2,4-dichlorobenzyl)oxy]phenethyl}-imidazole nitrate

Molecular formula and molecular mass: $C_{18}H_{14}Cl_4N_2O \cdot HNO_3$; 479.16

Structural formula:



Physicochemical properties: white, crystalline or microcrystalline powder, very slightly soluble in water (0.03%) and very slightly to slightly soluble in most common organic solvents and dilute inorganic acids.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Miconazole nitrate has been clinically effective in treating tinea pedis (athlete's foot), tinea cruris, tinea corporis, and tinea versicolor caused by dermatophytes. MONISTAT* Derm Cream is also effective in cutaneous candidiasis. Among the organisms against which MONISTAT* Derm Cream has been found effective are Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton interdigitale, Epidermophyton floccosum, Micosporum canis, Micosporum gypseum, species of Candida including C. albicans, and Maleassezia furfur.

It is used clinically in conjunction with vaginal ovules or suppositories in MONISTAT* 3 and 7 DUAL-PAKs, respectively when symptoms of vulvovaginal candidiasis are particularly extensive.

Early clinical improvement (1-2 weeks) has been seen in the treatment of infections caused by dermatophytes and Candida species and in mixed fugal infections, but resistant lesions may take longer to clear. Candida infections should be treated for two weeks and dermatophyte infections for one month in order to reduce the possibility of recurrence. If a patient shows no clinical improvement after 30 days of treatment, the diagnosis should be reconsidered.

Topical administration of MONISTAT* miconazole nitrate cream 2% has been effective in the local treatment of fungal infections of the skin and nails, including tinea pedis, tinea cruris, tinea corporis, as well as tinea versicolor. Clinical studies have involved several treatment periods but experience indicates that topical applications should continue for two weeks for tinea cruris, tinea corporis and tinea versicolor and for four weeks for tinea pedis, to lessen the probability of recurrence.

Intravaginal administration of MONISTAT* miconazole nitrate 2% for 7 days has been determined to be effective for the treatment of vulvovaginal candidiasis. Clinical experience has indicated that the administration of a small amount of MONISTAT* Derm miconazole nitrate 2% cream to the vulvar area when an intravaginal solid dosage form such as MONISTAT* 7 Vaginal Suppositories or MONISTAT* 3 Vaginal Ovules are being used provides the added benefit of the cream form for particularly severe external symptoms of itching and irritation.

14.2 Study Results

Please see Clinical Trials – Trials Design and Study Demographics Section.

14.3 Comparative Bioavailability Studies

Not applicable.

15 MICROBIOLOGY

1. In Vitro Antimicrobial Activity (see Tables 1, 2)

   Dermatophytes showed high suceptibility to miconazole nitrate at a concentration of 10 mg/ml. Amongst these were Microsporum canis, M. audouinii, M. gypseum, Trichophyton mentagrophytes, T. rubrum, T. tonsurans, T. verrucosum, T. interdigitale, T. ferrugineum, and T. violaceum, as well as Langeronia soudanensis and Epidermophyton floccosum. In most of the dermatophytes studied, growth was also completely inhibited by a 1mg/ml concentration of miconazole and marked fungistatic activity was still observed in some species at concentrations of 0.1 mg/ml.

   Yeasts were also sensitive. High fungistatic effect was observed at concentrations of 10 :g/ml and 100 :g/ml in all species studied except for Rhodotorula sp. and Candida tropicalis.

   The fungistatic activity of miconazole nitrate was examined in species of dimorphic fungi, agents of fungal mycetoma, Actinomycetales, Phycomycetes and various other fungi. Concentrations of 100 :g/ml were generally 100 % effective in preventing growth and at concentrations of 10 :g/ml only a few species were not completely inhibited in their growth.

   Sporothrix sp. and Cladosporium also proved susceptible to miconazole whereas Aspergillus sp. and Fusarium were less so.

   The active bactericidal (bacteriostatic) concentration of miconazole nitrate against all species tested was 10 :g/ml. Among those tested were Erysipelothrix insidiosa, Staphylococcus hemolyticus, Staphylococcus aureus, Streptococcus pyogenes,

Enterococcus, Bacillus subtilis, and Bacillus anthracis.

Bacteriostatic activity was also found against two strains of penicillin-resistant Staphylococcus aureus.

The drug was found devoid of any activity against gram-negative bacteria.

Table 1

Fungal Species	Lowest dose levels of miconazole inhibiting growth of stated fungal species after 14 days incubation (: g/ml)						
	1,000	100	10	1	0.1	0.01	0.001
Trichophyton mentagrophytes	=====	=====	=====	=====	---------		
Epidermophyton floccosum	=====	=====	=====	=====	---------		
Trichophyton ferrugineum	=====	=====	=====				
Trichophyton verrucosum	=====	=====	=====				
Trichophyton rubrum	=====	=====	=====				
Trichophyton violaceum	=====	=====	=====				
Microsporum canis	=====	=====	=====				
Langeronia (T) soudanensis	=====	=====	---------	---------			
Microsporum audouinii	=====	=====	---------				
Trichophyton interdigitale	=====	=====	---------				
Trichophyton tonsurans	=====	=====					
Microsporum gypseum	=====	=====					

===== miconazole complete inhibition
--------- marked inhibition

Table 2

Fungal Species	Lowest dose levels of miconazole inhibiting growth of stated fungal species after 14 days incubation (*in vitro*) - :g/ml						
	1,000	100	10	1	0.1	0.01	0.001
Blastomyces brasiliensis* (1)	======	======	======	======	======	======	
Blastomyces dermatitidis (2)	======	======	======	======	======	----------	
Blastomyces dermatitidis (3)	======	======	======	======	======	----------	
Histoplasma capsulatum (1)	======	======	======	======	======		
Blastomyces dermatitidis (4)	======	======	======	======			
Blastomyces dermatitidis (5)	======	======	======				
Madurella mycetomi*	======	======	======	======			
Cephalosporum recifei	======	======	----------				
Allescheria boydii	======	======	----------				
Madurella grisea	======	----------					
Streptomyces madurae*	======	======	======	======			
Streptomyces somaliensis	======	======	======	----------			
Streptomyces pelletierii*	======	======	======				

Nocardia asteroides	======	======	======				
Nocardia brasiliensis	======	======	---------				
Entomophtora coronata	======	======	======				
Basidiobolus meristosporus	======	======	----------				
Saprolegnia sp.	======	======					
Mortierella sp.	---------	----------					
Mucor sp.	---------	----------					
Rhizopus sp.							
Absidia ramosa							
Cladosporium werneckii**	======	======	======	======			
Cladosporium trichoides*	======	======	======	----------			
Sporothrix schenckii	======	======	======				
Phialophora pedrosoi**	======	======	======	----------			
Aureobasidium pullulans	======	======	----------				
Penicillium notatum	======	======					
Alternaria sp.	======	======	----------				
Aspergillus fumigatus	======	======					
Aspergillus niger	======	======					
Aspergillus flavus	======	----------					
Aspergillus nidulans	======	----------					
Geotrichum candidum	======	----------					
Scopulariopsis brevicaulis	----------	----------					
Phialophora verrucosa	----------						
Fusarium sp.	======						

* score after 4 weeks
** score after 3 weels
===== miconazole complete inhibition
--------- marked inhibition

(1) MP MP – Mycelial phase
(2) YP/SB YP – Yeast phase
(3) YP/BHI BHI – Brain heart infusion broth
(4) MP/SB SB – Sabouraud broth
(5) MP/BHI

2. In Vivo

Adult guinea pigs pretreated with alloxan (200 mg/kg, i.m.) and infected with Candida albicans received daily topical treatment with 1 g of ointment containing 2% miconazole, nystatin, or amphotericin B, for 14 days starting on the third day after infection.

Miconazole applied topically was effective in curing the lesions induced by C. albicans and was slightly superior to and faster-acting than nystatin and amphotericin B.

Oral doses of miconazole at 160 mg/kg and 40 mg/kg administered for 14 days were effective against Candida albicans-induced lesions. By comparison, oral nystatin and amphotericin B (160 mg/kg) and pimaricin (40 mg/kg) had little effect on the course of the infection.

Summary

Treatment	Dose	# of animals	Route	Lesion scores at 15 days* (no. of animals) 0 1 2 3 4
Controls	excipient	20	topical	0 4 6 7 3
Miconazole	2%	20	topical	1 11 4 3 1
Nystatin	2%	20	topical	0 4 7 7 2
Amphotericin B	2%	20	topical	0 2 4 7 7
Controls	excipient	15	oral	0 1 1 6 7
Miconazole	160 mg/kg	12	oral	10 2 0 0 0
Miconazole	40 mg/kg	14	oral	9 5 0 0 0
Miconazole	10 mg/kg	13	oral	2 2 1 5 3
Nystatin	160 mg/kg	6	oral	0 1 0 2 3
Amphotericin B	160 mg/kg	6	oral	0 0 1 2 3
Rimaricin	40 mg/kg	2	oral	0 0 0 0 2

* NOTE: Inhibition of growth was scored as follows (some spontaneous healing in controls by day 15)

0 = absence of lesions
1 = 1/4 the lesions of infected controls
2 = 1/2 the lesions of infected controls
3 = 3/4 the lesions of infected controls
4 = lesions corresponding to infected controls

Guinea pigs infected with Trichophyton (7 groups) were completely cured following topical treatment with 2% and 0.5% miconazole nitrate. Similar results were obtained for M. canis with 2% miconazole nitrate. Treatment initiated 3 days after infection was different only for M. canis where it proved less effective.

Orally, miconazole nitrate at 160 mg/kg was effective against T. mentagrophytes and six out of seven animals infected with M. canis were completely cured by day 28 (14 days after treatment). Does of 10 and 40 mg/kg orally were relatively ineffective.

16 NON-CLINICAL TOXICOLOGY

ANIMAL

1. Acute

Acute oral toxicity of miconazole (7-day mortality) was assessed in male white mice, male Wistar rats, female guinea pigs and male and female mongrel dogs. The compound was administered in a micronized aqueous suspension. The following values were obtained:

Species	LD_{50} (95% Confidence Limits) mg/kg
Mice	578 (324.4 – 1030)
Rats	> 640
Guinea Pigs	276 (201.2 – 378.3)
Dogs	> 160

The intraperitoneal LD50 in male Swiss Webster mice was 670 mg/kg + 0.36 S.E.

2. Subacute

Rats
Adult Wistar Rats (10 males and 10 females per dose group) were given miconazole at 80, 10 and 5 mg/kg/day in their diet for 13 weeks. All animals survived the test. The urine of treated animals was compared with the urine of control animals. Specific gravity was increased in the high dose group and urine pH was lowered in the intermediate and high dose groups. In addition, minor changes in liver, thymus, spleen and kidney were noted in the high dose group after histopathological examination. From these results the no-effect dose is calculated to be less than 80 mg/kg, but greater than 20 mg/kg.

Dogs
Adult Beagle dogs (3 males and 5 females per dose group) were given miconazole at 40, 20 and 2.5 mg/kg/day orally by capsule, 6 days a week, for 13 weeks. All animals survived the test. The following changes were noted: haematocrit and haemoglobin values were lowered in the high dose group; serum calcium and cholesterol and sulfhydryl values decreased in the intermediate and high dose groups and the odd animal in the high dose group salivated and would vomit subsequent to drug administration. At autopsy slight liver changes were noted in the high dose group animals. From these results the no-effect dose is calculated to be less than 40 mg/kg but greater than 10 mg/kg.

3. Chronic

Rats
Adult Wistar rats (30 males and 30 females per dose group) were given miconazole at 160, 40 and 10 mg/kg/day in their diet. Interim sacrifices of 20 animals (10 males and 10 females) per dose level were made at 6 and 12 months, the remaining animals being sacrificed at the termination of the study (18 months). Histopathology showed some slight liver changes which appeared to be more pronounced in the males. However, this finding did not progress with time. No other significant findings were reported and miconazole was well tolerated up to 160 mg/kg over the study period.

Dogs
Adult Beagle dogs (3 males and 3 females per dose group) were given oral doses by capsule of miconazole at 20, 5 and 1.25 mg/kg/day, 6 days a week for 52 weeks. All animals survived the study period. Persistent increased alkaline phosphatase levels and slightly increased SGPT values were noted with the high dose group; however, all other measured parameters were normal. At autopsy no significant histopathological changes were evident.

4. Reproductive Studies

Fertility in Rats
Adult Wistar rats (2 groups per dose level) were given miconazole at 320, 160 and 80 mg/kg in their diet as follows:

Group A: 20 males - drug given 60 days premating, 20 females - no drug
Group B: 20 males - no drug, 20 females - drug 14 days premating plus 21 days gestation

Females were sacrificed at day 22 of gestation. There was no difference between dose levels or groups A or B in pregnancy rate, but the number of dead foetuses and resorbed foetuses was

increased in the high dose level. No abnormalities were noted among pups born to dosed females with the exception of two animals with rib deformities born to a high dose female. Based on the study findings, miconazole had no effect on the fertility of dosed males or females.

Peri-and Postnatal Studies in Rats
In one study, pregnant rats (20 animals per dose group) were given miconazole at 320, 160 and 80 mg/kg in their diet from day 16 of gestation through the 3 week lactation period. The gestation period was increased one day for the intermediate and high dose groups. In the test animals, litter size and the number of live foetuses at birth were slightly lower when compared to controls. In addition, body weight gains in the intermediate and high dose groups for the surviving pups were lower, whereas the birth weights of pups in the various groups had not differed.

In a second study pregnant Long-Evans derived rats (20 animals per dose group) were given miconazole, suspended in carboxymethylcellulose at 80, 40 and 20 mg/kg by gastric gavage from day 14 of gestation through to day 21 post partum. In the high dose group a prolonged gestation period associated with an increase in the number of still born pups was noted. Performance of the other dose groups was comparable to controls.

5. Teratology

Rats
Pregnant rats (20 animals per dose group) were given miconazole at 160 and 80 mg/kg in their diet from day 6 to day 15 of gestation. On day 22 of gestation, foetuses were delivered by caesarean section. No abnormalities were noted in this study either in the offspring or the reproductive performance of the dams.

Rabbits
Pregnant New Zealand white rabbits were given miconazole in carboxymethylcellulose at 80 (17 animals), 40 (15 animals) and 20 (15 animals) mg/kg by gavage from day 7 to day 19 of gestation. On day 30 of gestation, the animals were sacrificed. No adverse effect was noted at the low or intermediate dose levels upon maternal mortality, pregnancy rate or early parturition or on foetal resorption, size, sex ratio or malformation. At the high dose level there was evidence of maternal and foetal toxicity as indicated by maternal weight loss during gestation, lengthened period of gestation and significant foetal resorption. However, at the high dose there was no indication of teratogenicity.

6. Other Studies

Intravaginal irritation studies have been carried out in rabbits for 10 days with miconazole nitrate in the glycerides base suppository formulation (100 mg per suppository single daily dose). Under the experimental conditions the glycerides base with or without miconazole nitrate has demonstrated a low order of irritation to the intact vaginal mucosa.

Similar findings were reported for vaginal irritation studies in rabbits and monkeys (3 months) utilizing 1 gm carbowax suppositories containing miconazole nitrate 2% and in rabbits for periods ranging from 10 days to 3 months with miconazole nitrate in its 2% cream formulation (single daily dosage of 1 gm of cream; 5-7 mg/kg of miconazole). No evidence of systemic toxicity was noted.

Dermal and ocular studies on rabbits ranging from 24 hours to 1 month in duration have

revealed little irritation when miconazole was utilized in the 2% cream formulation. Dose levels of miconazole in these studies were as high as 50 mg/kg/day. In addition, no evidence of systemic toxicity was apparent in these studies.

An ocular irritation study of miconazole nitrate formulated with mineral oil, white wax and liquid petrolatum was performed in rabbits for four weeks. The results indicate that this 2% miconazole nitrate formulation when instilled into the eye once daily at a 0.1 mL dosage produces no irritation.

17 SUPPORTING PRODUCT MONOGRAPHS

Not applicable.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

MONISTAT* Derm Cream
Miconazole Nitrate Vaginal Cream 2%

Read this carefully before you start using **MONISTAT* Derm Cream** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MONISTAT* Derm Cream**.

Serious Warnings and Precautions

- Should not be used for self-medication if vaginal itching or discomfort is occurring for the first time;
- Should not be used for self-medication if fever, nausea, unexplained pain in the lower back, lower abdomen, or either shoulder, or foul-smelling vaginal discharge are present;
- Discontinue use if sensitization or other signs of irritation not present before therapy occur;
- Should not be used by pregnant or nursing women without consulting health professional;
- Avoid intercourse during therapy;
- Therapy reduces the effectiveness of latex condoms and diaphragms;
- Should not be introduced into the eyes;
- Blood thinning effect;
- Consult a doctor if you do not respond to therapy as the symptoms you are having may be those of a more serious condition.

What is MONISTAT* Derm Cream used for?

MONISTAT* Derm Cream is indicated for:

- the relief of external vaginal itching and irritation

How does MONISTAT* Derm Cream work?

This cream works by relieving the external itching and irritation associated with yeast infection.

What are the ingredients in MONISTAT* Derm Cream?

Medicinal ingredients: Miconazole Nitrate
Non-medicinal ingredients: Benzoic Acid, Cetyl Alcohol, Isopropyl Myristate, Polysorbate 60, Potassium Hydroxide, Propylene Glycol, Stearyl Alcohol, Water

MONISTAT* Derm Cream comes in the following dosage forms:

Cream, 2%

Do not use MONISTAT* Derm Cream if:

- hypersensitive to this drug or to any ingredient in this formulation, including any non-medicinal ingredient, or component of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MONISTAT* Derm Cream. Talk about any health conditions or problems you may have, including if you:

- experience sensitization or marked irritation (rash, burning, blistering, redness) not present before therapy occur
- introduce MONISTAT* Derm Cream into the eyes
- take oral anticoagulants (blood thinning medication), such as warfarin, as bruising or bleeding may occur

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MONISTAT* Derm Cream:

- oral anticoagulants (blood thinning medication), such as warfarin

How to use MONISTAT* Derm Cream:
Use only in conjunction with MONISTAT® vaginal OVULE™ and vaginal suppositories.

Apply a thin layer of cream to the itchy or irritated genital area in the morning and evening as needed. Massage gently until the cream disappears.

Usual dose:
Use morning and evening as needed, up to 7 days as long as external symptoms persist.

Overdose:

Monistat* Derm Cream is intended for external application and not for oral use. If swallowed, call a poison control centre or get medical help right away.

If you think you have used too much Monistat* Derm Cream, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Monistat* Derm Cream contains a cream that is to be used morning and evening for as long as external symptoms persist. If you miss a dose of the cream, you do not need to make up the missed dose. Skip the missed dose and continue with your next dose.

What are possible side effects from using MONISTAT* Derm Cream?

These are not all the possible side effects you may have when taking MONISTAT* Derm Cream. If you experience any side effects not listed here, tell your healthcare professional. On rare occasions it has been reported that patients treated with MONISTAT* Derm Cream

experienced mild itchy skin, irritation and burning at the site of application.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE Mild itchy skin	X		
Irritation	X		
Burning at the site of application	X		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Monistat* Derm Cream should be stored at controlled room temperature (15 °C - 30 °C).

Keep out of reach and sight of children.

If you want more information about MONISTAT* Derm Cream:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.monistat.ca, or by calling 1-800-891-4857

This leaflet was prepared by Insight Pharmaceuticals LLC

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