PRODUCT MONOGRAPH

Micatin®miconazole nitrate cream 2% USP
Miconazole nitrate cream USP, 2%

Micatin® powder spray – unscented 2% Miconazole nitrate USP
aerosol, 2%

Antifungal Agent

WellSpring Pharmaceutical Canada Corp.
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Control Nos. 235783 and 235806

PRODUCT MONOGRAPH

Micatin® miconazole nitrate cream 2% USP

Micatin® powder spray - unscented 2%

Therapeutic Classification

Antifungal Agent

CLINICAL PHARMACOLOGY

Miconazole nitrate exhibits broad spectrum in vitro fungistatic activity; for example, against species of the genus Candida. Studies with Candida albicans (strain R.V. 4688) indicate that at low concentrations, miconazole nitrate acts primarily on the yeast cell membrane resulting in selective inhibition of the uptake of precursors of RNA and DNA (purines) and mucopolysaccharide (glutamine).

In addition, in vitro antibacterial activity has been reported (gram-positive baccilli and cocci).

INDICATIONS AND CLINICAL USE

Micatin® is indicated for the topical treatment of dermatophytes and Candida infections and also lesions caused by mixed infections involving susceptible fungi. It has been clinically effective in treating tinea pedis (athlete's foot), tinea cruris (jock itch), tinea corporis (ringworm), and tinea versicolor (fungal infection of the skin) caused by dermatophytes.

Micatin® is also effective in cutaneous candidiasis (skin infections caused by candida fungi), excluding moderate to severe candidal paronychia (inflammation and infection of the nail folds caused by candida fungi). Among the organisms against which Micatin® has been found effective are Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton interdigitale, Epidermophyton floccosum, Microsporum canis, Microsporum gypseum, species of Candida including C. Albicans, and Malassezia furfur.

CONTRAINDICATIONS

Ask a doctor or pharmacist before use if you are taking the prescription blood thinning medicine warfarin, because bleeding or bruising may occur.

WARNINGS AND PRECAUTIONS

Ask a doctor or pharmacist before use if you are taking the prescription blood thinning medicine warfarin, because bleeding or bruising may occur.

Ask a doctor or pharmacist before use if you are pregnant, trying to get pregnant, or breastfeeding.

If irritation occurs, or there is no improvement following the full treatment period (see Dosage and Administration), discontinue use and see a doctor.

Avoid contact with the eyes; if this happens, rinse thoroughly with water.

For external use only.

Do not use in children under 2 years of age unless directed by a doctor.

Keep out of reach of children. If swallowed, call a poison control centre or a healthcare professional immediately.

Do not use for scalp and nail infections.

ADVERSE REACTIONS

On rare occasions it has been reported that patients treated with Micatin® experience mild pruritus, irritation and burning at the site of application.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

None known.

DOSAGE AND ADMINISTRATION

Cleanse skin with soap and water and dry thoroughly. Apply (or spray) a thin layer over the affected area 2 times a day, morning and night for the full treatment period. If there is no improvement within 2 weeks a physician should be consulted. Otherwise, continue treatment for 1-2 weeks after symptoms have disappeared up to a maximum of 4 weeks. Jock itch and ringworm usually require 2 weeks to resolve, while athlete's foot may require 4 weeks.

When treating athlete's foot pay special attention to the spaces between toes; wear well fitting, ventilated shoes and cotton socks.

Micatin® miconazole nitrate cream 2% USP should be applied sparingly and smoothed in well to avoid maceration effects. The treated area should be massaged gently until the Micatin® miconazole nitrate cream 2% USP disappears.

Early clinical improvement (1-2 weeks) has been seen in the treatment of infections caused by common dermatophytes and Candida species, but resistant lesions may take longer to clear. Candida infections should be treated for two weeks.

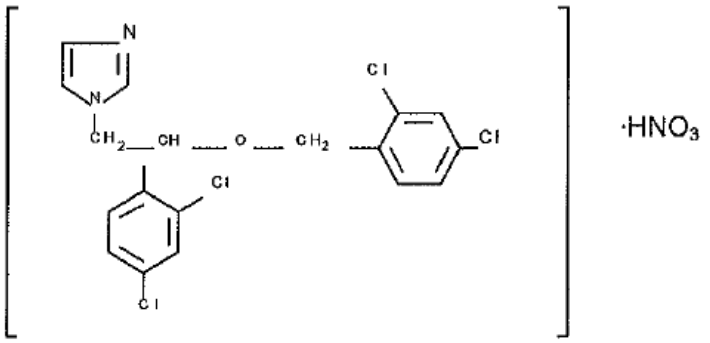
If a patient shows no clinical improvement after the full treatment period, the diagnosis should be reconsidered.

PHARMACEUTICAL INFORMATION

Proper Name: Miconazole Nitrate

Chemical Name: 1-{2,4-dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl}-imidazole mononitrate.

Structural Formula:



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

Molecular Weight: 479.16

Description:

Miconazole nitrate is a white, crystalline powder. It is very slightly soluble in water (0.03%), and very slightly to slightly soluble in most common organic solvents and diluted solutions of inorganic acids.

Composition:

Micatin® miconazole nitrate cream 2% USP is a water miscible, white cream containing 2% miconazole nitrate as the active ingredient.

Nonmedicinal ingredients (alphabetical): benzoic acid, butylated hydroxyanisole, mineral oil, peglicol 5 oleate, pegoxol 7 stearate, purified water.

Micatin® powder spray - unscented 2% contains miconazole nitrate 2% (as a percent of non-volatile ingredients). Nonmedicinal ingredients (alphabetical): alcohol, hydrocarbon propellant, stearalkonium hectorite, sorbitan sesquioleate, talc.

Stability and Storage Recommendations:

Micatin® should be stored at controlled room temperature (15°C – 30°C).

AVAILABILITY OF DOSAGE FORMS

Micatin® miconazole nitrate cream 2% USP is supplied as 2% miconazole nitrate cream in 30 gram tubes.

Micatin® powder spray - unscented 2% is supplied as 2% miconazole nitrate in 85 g or 120 g containers.

MICROBIOLOGY

A. In Vitro Antimicrobial Activity: (see tables 1,2).

Dermatophytes showed high susceptibility to miconazole nitrate at a concentration of 10 µg/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 1 µg/ml concentration of miconazole and marked fungistatic activity was still observed in some species at concentrations of 0.1 µg/ml.

Yeasts were also sensitive. High fungistatic effect was observed at concentrations of 10 µg/ml and 100 µg/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 µg/ml were generally 100% effective in preventing growth and at concentrations of 10 µg/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 µg/ml. Among those tested were Erysipelothrix insidiosa, Staphylococcus hemolvticus, 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						
	1,000	100	10	1	0.1	0.01	0.001 µg/mL
Trichophyton mentagrophytes	=======	=======	-------	-------	----------		
Epidermophylon 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 inhibition growth of stated fungal species after 14 days incubation (in vitro)						
	1,000	100	10	1	0.1	0.01	0.001 µg/mL
Blastomyces brasiliensis* (1)	==========	==========	==========	==========	==========	==========	
Blastomyces dermatitidis (2)	==========	==========	==========	==========	==========	----------	
Blastomyces dermatitidis (3)	==========	==========	==========	==========	==========	----------	
Histoplasma capsulatum (1)	==========	==========	==========	==========	==========		
Blastomyces dermatitidis (4)	==========	==========	==========	==========			
Blastomyces dermatitidis (5)	==========	==========	==========				
Madurella mycetomi*	==========	==========	==========	==========			
Cephalosporum recifei	==========	==========	----------				
Atlescherla boydii	==========	==========	----------				
Madurella grisea	==========	----------					
Streptomyces madurae*	==========	==========	==========	==========			
Streptomyces somaliensis	==========	==========	==========	----------			
Streptomyces pelletierilli*	==========	==========	==========				
Nocardia asteroides	==========	==========	==========				
Nocardia brasiliensis	==========	==========	----------				
Entomophlora coronata	==========	==========	=========				
Basidiobolus meristosporum	==========	==========	----------				
Saprotegnia sp.	==========	==========					
Mortierella sp.	----------	----------					
Mucor sp.	----------	----------					
Rhizopus sp.							
Absidia ramose							
Cladosporium werneckii**	==========	==========	==========	==========			
Cladosporium trichoides*	==========	==========	==========	----------			
Sporothrix schenckii	==========	==========	==========				
Phlafophora pefrosoi**	==========	==========	==========	----------			
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 ===== complete inhibition - - - - - - marked inhibition

** score after 3 weeks

(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

B. 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. (See Table 3)

TABLE 3

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 = 314 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 of treatment). Doses of 10 and 40 mg/kg orally were relatively ineffective.

PHARMACOLOGY

ANIMAL

1. Tissue and Whole Animal

The agonist activity 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-a-adrenergic (rabbit spleen) and β-adrenergic blocking (fowl rectal caecum) activity.

Miconazole given to mice in a single dose of 40 mg/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.

2. Metabolism and Pharmacokinetics

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

Rats *(miconazole tritium labelled at C-2 of the imidazole ring)*.

Five male Wistar rats were each given an oral dose of 40 mg/kg miconazole in PEG-200. During the four days in which urine and faeces were collected, 66% of the total radioactivity administered was collected (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 α-(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 (0.5mL of 1% formulation). In the excretion studies urine and faeces were collected for 12 days from the dogs and urine only from 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 µg/mL) was found with the carbowax vehicle as was the case with rabbits (0.17 - 10.8µg/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 β-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 is recovered in 2-3 days and found in the faeces. Maximum blood levels of tritium occured 6 hours after dosing (0.95 µg/mL).

Human

The absorption, metabolism and excretion of orally, intravaginally and topically administered labelled miconazole nitrate was observed in healthy normals. Blood, urine and faecal samples were taken. The study indicated that the absorption and excretion of miconazole administered orally was unrelated to dosage and duration of treatment. Intravaginal and topical administration indicated low absorption. Eight hours after topical examination, 90% of the drug was recovered from the skin.

TOXICOLOGY

Animal

1. Acute

Acute oral toxicity of miconazole (7-day mortality) was assessed in male white mice, male Wistar rats, female ginea 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 LD_{50} in male Swiss Webster mice was 670 mg/kg $\pm$ 0.36 (S.E.M.).

2. Subacute

Rats

Adult Wistar Rats (10 males and 10 females per dose group) were given miconazole at 80, 20 and 5 mg/kg/day in their diet for 13 weeks. All animals

survived the test. Comparing the dose levels to control, urine specific gravity was increased in the high dose group, urine pH was lowered in the intermediate and high dose groups, and small changes in liver, thymus, spleen and kidney were noted in the high dose group after histopathological examination. From the 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, 10 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 groups decreased in the intermediate and high dose groups; alkaline phosphatase was elevated in the high dose group 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.

5. *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. As well, 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.

6. 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 (CMC) 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, increased parturition and significant foetal resorption. However, at the high dose there was no indication of teratogenicity.

7. Other Studies

Intravaginal irritation studies have been carried out in rabbits for periods ranging from 10 days to 3 months. Miconazole in its cream formulation (2%) and placebo cream were installed daily at a dosage of 1 gm of cream formulation (5-7 mg/kg of miconazole). Under the experimental conditions the cream base with or without miconazole showed a low order of irritation to the intact vaginal mucosa. No evidence of systemic toxicity was noted. Similar findings were reported for vaginal irritation studies with rabbits and monkeys (3 months) utilizing 1 mg carbowax suppositories containing miconazole (2%).

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 has been apparent in these studies.

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