PRODUCT MONOGRAPH

MONISTAT* 3 Vaginal Cream
miconazole nitrate cream 4% (w/w) USP

Antifungal Agent

ATC code: G01A F04

Insight Pharmaceuticals Corp.
Langhorne, PA, U.S.A. 19047-1749

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Therapeutic Classification

Antifungal Agent

CLINICAL PHARMACOLOGY

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.

In *Candida albicans*, miconazole nitrate inhibits the transformation of blastospores into invasive mycelial form. 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.

INDICATIONS AND CLINICAL USE

MONISTAT*3 (miconazole nitrate 4%) Vaginal Cream is indicated for the local treatment of vulvovaginal candidiasis (moniliasis).

Although vulvovaginal candidiasis may be more difficult to cure during pregnancy, pregnant patients can be treated with the same regimen as non-pregnant patients. The 3-day regimen (MONISTAT* 3) is preferred, with the 1 or 7-day regimens (MONISTAT* 1 or MONISTAT* 7) providing effective alternatives.

No significant difference in therapeutic cure rate (therapeutic cure includes both symptomatic and microbiological cure) was reported between the pregnant and non-pregnant patient groups who participated in clinical evaluations of the 3-day (ovules) or 7-day (suppositories or cream) treatment regimens.

Similarly, users and non-users of oral contraceptives who participated in these clinical evaluations experienced therapeutic cure rates which did not differ significantly.

In addition, no statistically significant differences in therapeutic cure rates were noted between patients undergoing dosage regimens of varying duration (1, 3, 7, 10, and 14 day).

CONTRAINDICATIONS

Patients known to be hypersensitive to this drug or any of its ingredients.

PRECAUTIONS

1. Patients should not use MONISTAT* vaginal preparations 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.
2. Patients should not use MONISTAT* vaginal preparations for self-medication if pain in the back or lower abdomen, fever or malodorous vaginal discharge are present, as a condition more serious than vulvovaginal candidiasis may exist.

3. Patients should be advised to discontinue medication if sensitization or other signs of irritation (rash or hives, burning, blistering, redness) not present before therapy occur.
4. 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.
5. Pregnant patients should be advised to exercise caution in the use of the vaginal applicator.
6. 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. During therapy it may be advisable to instruct the patient to abstain from intercourse.
8. MONISTAT* 3 Vaginal Cream (4%) reduces the effectiveness of latex condoms and diaphragms. Therefore concurrent use of MONISTAT* 3

Vaginal Cream with natural rubber products such as vaginal diaphragms or condoms is not recommended.

9. Miconazole administered systemically is known to inhibit CYP3A4/2C9. Due to 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* due to the risk of bleeding and bruising. Caution should be exercised and the anticoagulant effect should be monitored [9, 10].

ADVERSE REACTIONS

The standard for defining frequency terms will be based on the Council for International Organizations of Medical Science (CIOMS) convention.

Specifically:

Very common	≥1/10 (≥10%)
Common	≥1/100 and <1/10 (≥1% and <10%)
Uncommon	≥1/1,000 and <1/100 (≥0.1% and <1%)
Rare	≥1/10,000 and <1/1,000 (≥0.01% and <0.1%)
Very rare	<1/10,000, including isolated reports (<0.01%)

In general, the complaints reported with miconazole nitrate therapy involved vulvovaginal burning, itching, irritation, pelvic cramping and edema as well as hives, rash and headache.

Clinical Trial Data

Two randomized clinical studies involving over 500 patients, comparing three-day treatment with MONISTAT* 3 Vaginal Cream (4%) to the seven-day cream treatment with MONISTAT*7 Vaginal Cream (2%), indicated that generally both

products were equally well tolerated. Both studies were double-blind, randomized, controlled, parallel group, comparative, multi-centre, Phase III studies of patients with documented vulvovaginal candidiasis. The most frequent adverse experiences reported in both treatment groups from either study were external genital pruritus, genital burning, headache, genital irritation, genital discharge, respiratory congestion, dysmennorhea, abdominal pain, nausea and upper respiratory infection. For each study, body systems with the highest incidence of adverse experience reporting (greater than 10% in either treatment group) were determined. Results from each study were combined and are displayed in the following table:

System Organ Class Adverse Event	% patients on Miconazole (**2% cream, 7 Day**) reporting AEs during 2 trials (n = 274)	% of patients on Miconazole (**4% cream, 3 day**) reporting Aes during 2 trials (n = 272)
Overall adverse events	--	--
Nervous System Disorders	22.1	19.0
Reproductive System and breast disorders	46.0	46.7
Gastrointestinal system disorders	14.7	11.3
Respiratory system disorders	11.4	10.9

Postmarketing data

Adverse events which may be causally related to the administration of MONISTAT* that have come to light as a result of reports received in relation to administration of the marketed product are provided in this section. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders
Allergic conditions, including anaphylactic and anaphylactoid reactions, angioneurotic edema

Skin and subcutaneous tissue disorders
Urticaria, pruritus, rash

Reproductive system and breast disorders
Pelvic pain (cramping), genital burning sensation, genital pruritus female, vaginal irritation, vaginal discharge

General disorders and administration site conditions
Application site reactions

SYMPTOMS AND TREATMENT OF OVERDOSAGE

MONISTAT* products are intended for local application and not for oral use. In case of accidental ingestion, contact a doctor or Poison Control Centre at once. Keep this and all other medications out of the reach of children and pets.

MONISTAT*3 Vaginal Cream (4%) contains 40 mg miconazole nitrate per 1 g of product, or a total of 600 mg in each package. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract. Hence, the maximum possible systemic exposure if the entire contents of the MONISTAT* 3 Vaginal Cream package were to be accidentally or deliberately ingested would be equivalent to 300 mg.

This compares favourably to the lowest IV dose administered to adults (600 - 1800 mg) and to the IV dose that would be administered to a one year old child (400 mg). Consequently, the possibility of acute overdosage is remote.

However, 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.

DOSAGE AND ADMINISTRATION

MONISTAT* 3 (miconazole nitrate 4%) Vaginal Cream: 5 grams (equivalent to 200 mg miconazole nitrate) administered intravaginally once daily at bedtime for three consecutive nights.

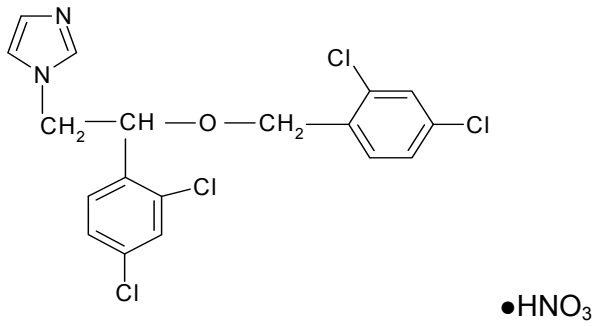
A course of therapy may be repeated if the patient remains symptomatic and if it has been determined by appropriate smears and cultures that the infecting organism is still miconazole susceptible *Candida*.

PHARMACEUTICAL INFORMATION

Proper Name: Miconazole Nitrate

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

Structural Formula:



●HNO_3

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

Molecular Weight: 479.16

Melting Point: 178 -184°C

Description: Miconazole nitrate is a 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.

Composition: MONISTAT* 3 Vaginal Cream contains 4% (40 mg per 1 g) of miconazole nitrate as the active ingredient. Nonmedicinal ingredients: benzoic acid, cetyl alcohol, isopropyl myristate, polysorbate 60, potassium hydroxide, propylene glycol, purified water, stearyl alcohol.

Stability and Storage Recommendations: MONISTAT* 3 Vaginal Cream should be stored at controlled room temperature (15°C - 30°C).

AVAILABILITY OF DOSAGE FORM

MONISTAT* 3 Vaginal Cream (miconazole nitrate 4%) is available in an individual package containing 3 prefilled applicators, each containing 5 g of cream.

INFORMATION FOR THE CONSUMER

MONISTAT* 3 Vaginal Cream in Prefilled Applicators

MONISTAT* 3

Prefilled Applicators

CURES MOST VAGINAL YEAST INFECTIONS

Thank you for purchasing MONISTAT* 3 Vaginal Cream in Prefilled Applicators. MONISTAT* 7, MONISTAT* 3 and MONISTAT* 1 products all provide an effective cure for most vaginal yeast infections. MONISTAT* Derm Cream is also available, to be used in conjunction with these MONISTAT* vaginal therapies, for the relief of particularly severe external itching and irritation associated with vaginal yeast infections. Please read the following information carefully and if you have any questions, call our toll free number, 1 800 891-4857, between 8:15 a.m. and 8:00 p.m. Eastern Time, Monday through Friday.

MONISTAT* products are available in the following forms:

MONISTAT* 1	Ovule or Combination Pack
MONISTAT* 3	Cream (Prefilled Applicator), Ovules or Combination Pack
MONISTAT* 7	Cream (Prefilled Applicator), Suppositories or Combination Pack
MONISTAT* Derm Cream	15 g or 30 g external antifungal cream

INDICATION

For the treatment of vaginal yeast infections (candidiasis).

WHAT IS A VAGINAL YEAST INFECTION?

A vaginal yeast infection is an imbalance in the vagina caused, most commonly, by an overgrowth of the yeast called *Candida albicans. Candida* is a common organism in the vagina. When an imbalance occurs, such as when the normal pH balance of the

vagina changes or when your hormonal balance changes, *Candida* can multiply. You can then get a vaginal yeast infection.

Some of the factors that can contribute to the development of a vaginal yeast infection are:

- Hormone level changes: menstrual cycle, pregnancy, birth control pills (with high estrogen), estrogen therapy (during menopause)
- Antibiotic use
- Uncontrolled diabetes
- Weakened immune system: HIV infection, corticosteroid therapy, chemotherapy
- Perfumed soaps, bubble baths, or douching
- Wet bathing suits, nylon underwear, and pantyhose can retain heat and moisture, creating an environment that encourages the growth of *Candida*.

SYMPTOMS OF VAGINAL YEAST INFECTIONS

There are many signs and symptoms of a yeast infection. They can include:

- Vaginal itching (ranging from mild to severe);
- A clumpy, white vaginal discharge that may look like cottage cheese[1];
- Vaginal soreness, irritation or burning, especially during intercourse;
- Rash or redness around the vagina.

[1]A yellow/green discharge or a discharge that smells “fishy” may indicate that you have something other than a yeast infection. If this is the case, you should talk to your doctor before using MONISTAT*.

FOR BEST RESULTS

1. Be sure to use for 3 days in a row even if your symptoms go away before the third day.

2. Use 1 applicator of cream at bedtime for 3 nights in a row, even during your menstrual period.
3. Dry the outside vaginal area thoroughly after a shower, bath or swim. Change out of a wet bathing suit or damp workout clothes as soon as possible. A dry area is less likely to encourage the growth of yeast.
4. Avoid perfumed soaps, bubble baths or douching which may cause vaginal irritation and upset the normal balance.
5. Wipe from front to rear (away from the vagina) after a bowel movement.
6. Do not scratch the affected area as this can cause more irritation.
7. Discuss with your doctor any medication you are now taking. Certain types of medication can make your vagina more prone to infection.
8. Wear cotton underwear. Nylon underwear and pantyhose can retain heat and moisture creating an environment that encourages the growth of *Candida*.
9. To prevent transmission of the infection, do not allow others to use your washcloth or towel.
10. If your male sexual partner has any penile itching, redness, or discomfort, he should talk to his doctor and mention that you are treating a yeast infection.

PRECAUTIONS

If you have any or all of the symptoms of a yeast infection (vaginal itching, burning, white discharge) and if at some time in the past your doctor has told you that these symptoms are due to a yeast infection, then use MONISTAT* as directed. If, however, you have never had these symptoms before, you should talk to your doctor so that your condition can be properly diagnosed.

This product is only effective in treating vaginal infections caused by yeast. It does not treat other infections and does not prevent pregnancy. Do not take by mouth.
Talk to your doctor if you have fever, pain in the back or lower abdomen, or foul-smelling vaginal discharge before or during the use of this medication. You may have a more serious condition.

Relief of symptoms should begin within 3 days, but if complete relief is not felt within 7 days, the infection worsens or your symptoms return within 2 months, then you may have something other than a yeast infection. You should talk to your doctor.

If you are pregnant or think you may be, or are breastfeeding, use this product only under the advice and supervision of a doctor.

Oral anticoagulants (blood thinning medication): If you are taking an oral blood thinning medication, such as warfarin, talk to a doctor or pharmacist before using MONISTAT* products, as bruising or bleeding may occur.

While side effects are rare, sometimes a temporary increase in redness, itching or burning can occur at the start of treatment. This will not reduce the effectiveness of the product. If you experience a temporary increase in burning with MONISAT* 3, you may want to use a MONISTAT* 7 therapy the next time you have a vaginal yeast infection. Talk to your doctor if burning persists or if any unusual symptoms develop.

If skin rash, hives, abdominal cramps or new irritation occurs, discontinue use and call your doctor. If you are sensitive or allergic to any MONISTAT* product, do not use without talking to your doctor first.

Tampons may absorb the medication, therefore do not use them, day or night, for 7 days after beginning treatment.

This medication reduces the effectiveness of latex condoms and diaphragms. Do not rely on them to prevent sexually transmitted diseases or pregnancy while using MONISTAT*.

If you are at increased risk for sexually transmitted diseases, have multiple partners or change partners often, talk to a doctor before starting each treatment.

This product should not be used by children under 12 years of age unless advised to do so by a doctor. Please keep this and all drugs out of the reach of children.

Each prefilled applicator is overwrapped for your protection. Do not use if the overwrap is missing or not sealed.

In case of accidental ingestion, call a doctor or Poison Control Centre at once.

STORAGE

Store at room temperature (15 - 30°C).

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DIRECTIONS FOR USE

Many women find it more comfortable to use this product just before going to bed as this will reduce vaginal leakage. To begin treatment:

1. Unscrew blue cap from prefilled applicator.

2. Insert plunger into prefilled applicator by placing small, pointed end of plunger into the grey hole at the other end of the applicator (i.e. not end that was covered by blue cap).
3. Stand, squat, or lie on your back with your knees bent. Hold the prefilled applicator at the plunger end. Gently insert the applicator into the vagina as far as it will comfortably go. Holding the applicator in place, gently depress the plunger. This will release the cream in the vagina. Remove the applicator and discard.
4. Repeat step 1 through 3 before going to bed on each of the next 2 evenings. You may want to use a deordorant-free mini-pad or pantyshield while using MONISTAT* as there may be some vaginal leakage.

Tampons may absorb the medication; therefore, do not use them, day or night, for 7 days after beginning treatment.

MICROBIOLOGY

1. *In Vitro*

SUSCEPTIBILITY OF CANDIDA SPECIES TO MICONAZOLE

SPECIES	MIC (μg/mL)*
Candida parapsilosis, Z40	0.01
C. pseudotropicalis, Z27, RV 11210	0.01
C. krusei, Z70, RV 11792	0.1
C. tropicalis, Z156	0.1
C. tropicalis, RV 10747	1.0
C. albicans, Z248, RV 4688, 502/9, B 1995L	1.0
C. parapsilosis, RV 14018	1.0
C. stellatoidea, RV 19133	1.0
C. pelliculosa, Z220	10.0
C. guillermondii, Z55	10.0
C. intermedia, 512/9	10.0
C. tropicalis, 502/9	10.0

* Determined in Sabouraud broth culture medium

Electron microscopic examination was performed on *C. albicans* after treatment *in vitro* with different doses of miconazole: 5 ng, 1 mg, 2 mg and 5 mg/mL of culture (CYG medium) harvested twenty four hours later. The ultrastructural data on the alterations induced by a low dose (5 ng/mL) of miconazole indicated that the drug exerts its effect primarily on the cell wall and plasmalemma. With higher doses, progressive degradation of cytoplasmic material was observed. Injured parts of the cellular material were sequestered from the rest of the cytoplasm and engulfed by the vacuole. The same degradation process was noted on the cell periphery. Necrosis of cells, characterized by the loss of their normal shape and by severe alterations of every substructure was prominent at higher dose levels.

These ultrastructural findings firmly substantiate the fungistatic activity at low doses and the fungicidal activity at higher doses of miconazole. From the morphologic point of view, a clear dose relationship was established.

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

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 ß-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

a) *In Vitro*

Rats (miconazole nitrate tritium labelled)

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 α-(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 healthy 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 8.0×10^3. 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 of normal subjects, of patients with chronic renal failure and of patients under haemodialysis treatment.

b) *In Vivo*

Studies were conducted using miconazole labelled with tritium 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 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 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 a-(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 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 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).

HUMAN

Vaginal Absorption Study

Miconazole Nitrate was administered as a 2% cream formulation for 14 consecutive days to 6 female patients (5 non-pregnant and 1 pregnant) with confirmed diagnosis of vulvovaginal candidiasis (positive 10% KOH smear and NICKERSON'S Medium culture). Patients were scheduled to have blood samples drawn pre-therapy and day 5, 10, 16, 22 and 44 for analysis of serum levels of unchanged miconazole.

The levels of systemic absorption of miconazole which occurred during the period of intravaginal administration of MONISTAT* Cream were minimal

(1.7 - 4.2 ng/mL).

A consistent cumulative absorption was not evident and serum levels of miconazole declined rapidly after drug administration was discontinued (1-3 days post-therapy levels ranged from 1.7 to 3.7 ng/mL; however, after day 9 post-therapy miconazole was not detectable in serum).

Another study of systemic absorption from a single dose of 5 grams of radiolabelled MONISTAT* Cream 2% applied intravaginally resulted in only about 1% of the total administered dose being recovered in the urine.

MONISTAT* 3 (miconazole nitrate 4%) Vaginal Cream was administered at a dose of 5 g (200 mg) for three consecutive nights to 14 healthy female volunteers. The maximum level of systemic absorption (Cmax) amounted to an average of 12.7 ng/mL following the 3-day dosing period, which indicates a systemic bioavailability of only about 1%. Comparison of blood levels at the end of the 3 vs. 1 day dosing periods showed minimal accumulation and increase in AUC, with Tmax (12.6 hrs) unchanged.

A published study which examined the systemic absorption of miconazole nitrate from a 1200mg miconazole nitrate vaginal ovule in healthy women found low but measurable serum concentrations which remained steady for about 36 hours and then slowly declined. Mean systemic bioavailability was about 1.4%.

Miconazole persists in the vagina for up to 72 hours after a single dose. Plasma concentrations of miconazole are measurable within 2 hours of administration in some subjects, with maximal levels seen 12 to 24 hours after administration. Plasma concentrations decline slowly thereafter and were still measurable in most subjects 96 hours post-dose. A second dose administered 48 hours later resulted in a plasma profile similar to that of the first dose.

The small amount of miconazole that is absorbed is eliminated predominantly in feces as both unchanged drug and metabolites over a four-day post-

administration period. Smaller amounts of unchanged drug and metabolites also appear in urine. The mean apparent elimination half-life is 57 hours.

Summary of Clinical Efficacy and Safety

Clinical studies of miconazole nitrate (MONISTAT* brand) administered intravaginally in a dose of 100 mg for 7 consecutive days in the form of a cream (5 grams of 2% cream) and as a vaginal suppository have been effective in yielding both mycological and clinical cure rates of approximately 80% - 90% for vulvovaginal candidiasis.

Three-day regimens using MONISTAT* vaginal ovules 400 mg or MONISTAT* vaginal cream 200 mg inserted intravaginally for 3 consecutive nights also yielded comparable mycological and clinical results.

A one-day regimen using 1200mg MONISTAT* vaginal ovules intravaginally for a single night has also been demonstrated to provide comparable efficacy and safety to 2% miconazole nitrate vaginal cream daily for 7 days.

In addition, in the treatment of vulvovaginal candidiasis the single dose 1200mg miconazole nitrate vaginal ovule regimen was shown in published studies to provide comparable efficacy to miconazole nitrate as 400mg vaginal ovules daily x 3 days, 100mg tampons daily x 5 days, 100mg vaginal inserts x 7 days, and to single dose clotrimazole 500mg vaginal inserts, single dose oral fluconazole 150mg, and oral ketoconazole 400mg daily x 5 days.

All miconazole nitrate regimens were well tolerated in clinical circumstances with mild vaginal itching, irritation and burning being the most frequent side effects observed.

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	**LD50 (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.

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), as well as in the new base formulation used for the miconazole nitrate (4%) Vaginal Cream. Under the experimental conditions these formulations have 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% or

4% cream formulations. 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. A similar study with the 4% vaginal cream formulations produced mild ocular irritation.

Additional studies demonstrated that miconazole nitrate (4%) vaginal cream is non-irritating to the penile mucosa of rabbits and has no potential to produce delayed contact sensitization when administered to the skin of guinea pigs.

HUMAN

1. Tolerance Study

Miconazole Nitrate in a 2% vaginal cream formulation or placebo cream was administered to female volunteers meeting the following criteria - adult, healthy, non-pregnant and free of vaginal pathology - twice daily for a period of 30 days for the purpose of comparing side effect patterns, defining any possible changes in hematologic and biochemical parameters and to ascertain the level of systemic absorption of miconazole from the vagina. Twenty-three subjects receiving active cream and 20 receiving placebo cream participated in this double-blind study.

Pre- and post-administration physical examination findings remained essentially unchanged.

Analysis of the findings of the daily vaginal examinations and patient complaints revealed that both the active and placebo creams were essentially non-irritating to the normal vaginal mucosa. All reports of vaginal itching or burning were mild in nature (7 subjects using active cream, 3 subjects using placebo cream).

A review of the laboratory reports indicated no consistent changes which would denote drug toxicity.

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