

PRODUCT MONOGRAPH

NEO-ZOL VAGINAL CREAM 1%
Clotrimazole Vaginal Cream USP 1%

NEO-ZOL VAGINAL CREAM 2%
Clotrimazole Vaginal Cream USP 2%
Antifungal Agent

Prestige Pharma Inc.
6565 Duncan Street
Montreal, Quebec
H4B 1#8

Date of Preparation:
November 13, 2015

Control #187895

PRODUCT MONOGRAPH

NEO-ZOL VAGINAL CREAM 1%

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THERAPEUTIC CLASSIFICATION

Antifungal Agent

ACTION

Clotrimazole acts primarily by damaging the permeability barrier in the cell membrane of fungi. Clotrimazole brings about inhibition of ergosterol biosynthesis, an essential constituent of fungal cell membranes. If ergosterol synthesis is completely or partially inhibited, the cell is no longer able to construct an intact cell membrane. This leads to death of the fungus.

Exposure of *Candida albicans* to clotrimazole causes leakage of intracellular phosphorus compounds into the ambient medium with a concomitant breakdown of cellular nucleic acids and potassium efflux. The onset of these events is rapid and extensive after exposure of the organism to the drug, and causes a time-dependent and concentration-dependent inhibition of fungal growth.

INDICATIONS

Neo-Zol Vaginal Cream 1% is indicated for the 6-day treatment of vaginal candidiasis and associated vulval candidiasis. Neo-Zol Vaginal Cream 2% is indicated for the 3-day treatment of vaginal candidiasis and associated vulval candidiasis.

CONTRAINDICATIONS

Neo-Zol Vaginal Cream is contraindicated in patients who are hypersensitive to clotrimazole or any nonmedicinal ingredients in the formulation of Neo-Zol vaginal cream. For a complete listing, see the Composition section of the product monograph.

PRECAUTIONS

Neo-Zol Vaginal Cream is not for ophthalmic use. Neo-Zol Vaginal Cream is not for oral use.

As with all topical agents, skin sensitization may result. Use of Neo-Zol topical preparations should be discontinued should such reactions occur, and appropriate therapy instituted.

Treatment during the menstrual period should not be performed. The treatment should be finished before the onset of menstruation. Concomitant medication with vaginal Clotrimazole and oral tacrolimus (immunosuppressant) might lead to increased tacrolimus plasma levels. Patients should thus be thoroughly monitored for symptoms of tacrolimus overdose.

Use in Pregnancy

Although intravaginal application of clotrimazole has shown negligible absorption from both normal and inflamed human vaginal mucosa, Neo-Zol Vaginal Cream should not be used in the first trimester of pregnancy unless the physician considers it essential to the welfare of the patient.

The use of applicators may be undesirable in some pregnant patients and digital insertion of the vaginal tablets may be considered. Sanitation of the birth canal should be ensured particularly during the last 4 – 6 weeks of pregnancy.

ADVERSE REACTIONS

Experimental, therapeutic, and large scale clinical studies have shown clotrimazole to be well tolerated after topical application.

Erythema, stinging, blistering, genital peeling, edema, discomfort within the reproductive system and breasts, pruritus, allergic reaction (syncope, hypotension, dyspnea, urticaria), general irritation of the skin, pelvic pain and abdominal pain have been reported infrequently.

Two of 419 (0.5%) patients treated with the 1% vaginal cream experienced adverse reactions judged to be possibly drug related. These were intercurrent cystitis and vaginal burning. Neither necessitated discontinuation of treatment. None were of serious consequence and no complications occurred.

In clinical trials, 2/217 patients (0.9%) who received 2% clotrimazole vaginal cream experienced an adverse reaction. 26/796 (3.3%) of patients in clinical trials involving 10% clotrimazole vaginal cream experienced an adverse reaction. Most adverse reactions involved local itching and burning. Only rarely was it necessary to discontinue treatment.

DOSAGE AND ADMINISTRATION

Vaginal Candidiasis

NEO-ZOL VAGINAL CREAM 1%

The recommended daily dose is ONE full applicator intravaginally for SIX consecutive days, preferably at bedtime.

NEO-ZOL VAGINAL CREAM 2%

The recommended daily dose is ONE full applicator intravaginally for THREE consecutive days, preferably at bedtime.

Vaginal Candidiasis may be accompanied by irritation in the vaginal area. Therefore, concomitant local treatment with Neo-Zol Vaginal Cream applied to the irritated vaginal area and as far as the anal region twice a day is advisable. Neo-Zol Vaginal Cream applied on the glans penis may prevent reinfection by the partner.

N.B.: The cream should be inserted deep intravaginally by means of the applicator (See WARNING). The plunger should then be depressed slowly.

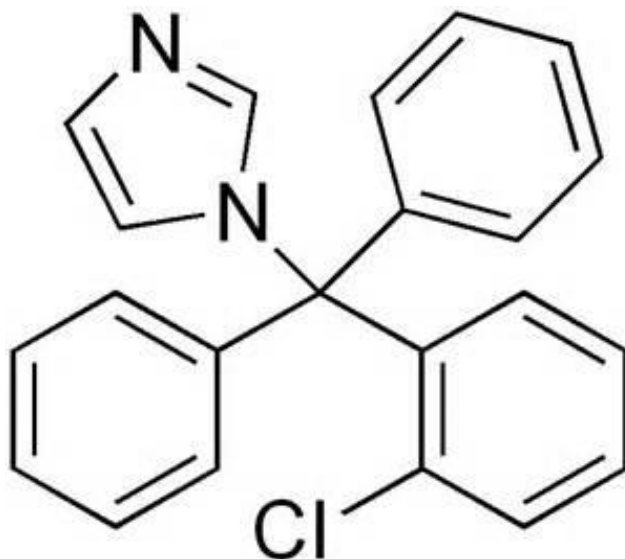
General hygienic measures such as twice daily tub baths and avoidance of tight underclothing are important in vaginal infections.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

PROPER NAME: clotrimazole
CHEMICAL NAME: 1-(o-chloro- α -diphenylbenzyl) imidazole

STRUCTURAL FORMULA:



MOLECULAR FORMULA: C₂₂H₁₇ClN₂ **Molecular Weight:** 344.84

Description:

Clotrimazole is a white to pale yellow, crystalline, weakly alkaline substance, M.P. 145°C, soluble in acetone, chloroform and ethanol, and practically insoluble in water. It forms stable salts with both inorganic and organic acids. It is not photosensitive but slightly hygroscopic and may be hydrolyzed in acid media.

COMPOSITION

Neo-Zol Vaginal Cream 1% contains 10 mg/g of clotrimazole in a cream base of sorbitan monostearate, polysorbate 60, cetyl esters wax, cetostearyl alcohol, 2-octyl dodecanol, purified water, and benzyl alcohol 1% as preservative.

Neo-Zol Vaginal Cream 2% contains 20 mg/g of clotrimazole in a cream base of sorbitan monostearate, polysorbate 60, cetyl esters wax, cetostearyl alcohol, 2-octyl dodecanol, purified water, and benzyl alcohol 1% as preservative.

STABILITY AND STORAGE RECOMMENDATIONS

Neo-Zol Vaginal Cream 1% and 2% must be stored at room temperature between 15oC and 30oC.

AVAILABILITY OF DOSAGE FORMS

Neo-Zol Vaginal Cream 1% is supplied in a 50 g tube of 1% vaginal cream in a carton containing disposable plastic applicators and patient instructions. 50 g of Neo-Zol Vaginal Cream 1% is sufficient for 6 intravaginal applications with additional cream for extravaginal use if required.

Neo-Zol Vaginal Cream 2% is supplied in a 25 g tube of 2% vaginal cream in a carton containing disposable plastic applicators and patient instructions. 25 g of Neo-Zol Vaginal Cream 2% is sufficient for 3 intravaginal applications with additional cream for extravaginal use if required.

INFORMATION FOR THE CONSUMER

EDUCATIONAL BROCHURE

NEO-ZOL VAGINAL CREAM 1%

Clotrimazole Vaginal Cream USP 1% **Antifungal**

FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS

READ THIS BEFORE USING

1. What is a "yeast infection"?

A "yeast infection" may occur any time there is an overgrowth of yeast organisms in the vagina. The vagina normally has bacteria and yeast organisms present. Under some conditions, the number of yeast organisms rises, irritating the delicate tissues of the vagina and vaginal opening. Conditions that make this more likely to occur are illness and the use of antibiotics (antibiotics do not affect the yeast organism). Changes in hormone levels may also increase the risk of a yeast infection. Changes that can occur during pregnancy, with the use of oral contraceptive pills, or just before a woman's period, may all increase the risk of a vaginal yeast infection. Some diseases, such as diabetes, can also make a person more susceptible. Even such things as hot humid weather, continuous use of panty liners, or tight, non-breathing clothing may increase a woman's chances of developing a yeast infection. These infections are not usually transmitted through sexual relations, even though a small percentage of male partners do have infections at the same time.

2. How do I know if I have a "yeast infection?"

When a "yeast infection" occurs, the body responds with an increase in vaginal secretions. These secretions are generally thick and sticky, but odourless. These are often referred to as "cheesy" or "curd-like" because of their similarity to cottage cheese. These secretions are irritating to the tissues of the vaginal area, causing intense itching, redness, and swelling. Sometimes red spots or sores may develop, especially if the area has been scratched in response to the itching. Soreness in the vagina, discomfort when passing urine and pain during sexual relations is common. Yeast infections do not cause fevers, chills, nausea, vomiting, diarrhoea, back pain, shoulder pain or vaginal haemorrhaging. If these symptoms are present, or if the vaginal discharge is foul-smelling, a more serious condition may be present and you should consult your physician immediately. Even if all of your symptoms point to a yeast infection, you should not attempt to treat yourself without consulting a physician if it is your first infection. If you have a second infection in less than 2 months, or experience frequent infections, contact your physician for evaluation and advice.

3. How do I cure a "yeast infection"?

To cure a "yeast infection", it is necessary to kill the overgrowth of yeast organisms that cause the infection. Neo-Zol can cure most vaginal yeast infections. Even though the

symptoms of an infection may be relieved in only a few hours or days, you should use Neo-Zol for a full 6 days. This will decrease the chance of the infection returning. If your symptoms do not improve after 3 days of treatment or disappear within 7 days, or if they get worse, discontinue treatment and contact your physician.

4. How do I use Neo-Zol Vaginal Cream 1%?

Neo-Zol Vaginal Cream 1% is used to treat vaginal yeast infections. Neo-Zol is inserted high into the vagina once a day (preferably at bedtime) for 6 consecutive days. Sufficient cream is provided for 6 intravaginal applications. Extra cream is supplied for use in relieving the external itching and burning sometimes associated with a vaginal yeast infection. Neo-Zol is only for use in the vagina and irritated vaginal area and should never be taken by mouth. Treatment during the menstrual period should not be performed. While you may have sexual relations during treatment with Neo-Zol, most couples wait until treatment has finished.

Filling the Applicator:

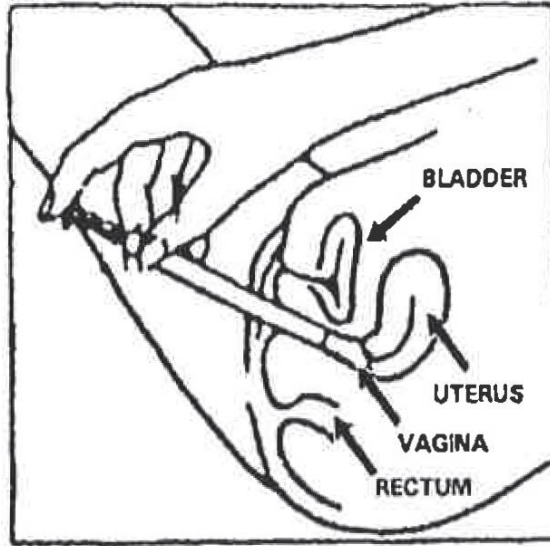
Remove the cap from the tube of Neo-Zol and reverse it to puncture the safety seal over the end of the tube. To fill the applicator, screw the open end of the applicator on the end of the tube. Gently squeeze the tube. The plunger will rise as cream enters the applicator. When the applicator is full, the proper amount of Neo-Zol has been pushed into the applicator and the applicator may be removed. Replace the cap and roll up the tube from the bottom so that the tube will be ready for the next use.

Inserting the Medication:

Neo-Zol Vaginal Cream 1% is inserted into the vagina in much the same way as a tampon. Stand, squat, or lie on your back in a comfortable position. Insert the filled applicator into the vagina as far as it will comfortably go. Holding the barrel of the applicator steady, gently depress the plunger until it stops. This will release the medication high in the vagina where it will be most effective. Remove the applicator. A small additional amount of Neo-Zol Vaginal Cream may be applied to the opening of the vagina to help provide extra relief.

Using the Cream Externally:

A small amount of Neo-Zol Vaginal Cream may be applied to the opening of the vagina to help provide extra relief of external symptoms. Squeeze a small amount of cream onto your finger and gently spread over the irritated vaginal area. Use the cream once or twice a day and only during the period when external symptoms are present, to a maximum of 7 days.



Disposing of the Applicator:

The Neo-Zol vaginal applicator is recyclable where facilities exist. 10

WARNINGS

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

If this is your first yeast infection, it should be evaluated by your physician before you start any medication.

Do not use Neo-Zol if you have abdominal pain, fever or a foul-smelling vaginal discharge. If these symptoms are present, you could have a more serious condition and should consult your physician immediately.

If there is no improvement in your symptoms in 3 days or if they have not disappeared within 7 days, you might not have a vaginal yeast infection. Consult your physician.

If you have frequent vaginal infections, or if your yeast infection returns in less than 2 months, consult your physician prior to starting treatment.

Do not use Neo-Zol if you are pregnant, think you are, or are nursing, without first consulting your physician.

If you experience a rash or new irritation while using the product, discontinue use and contact your physician.

Concomitant medication with vaginal Clotrimazole and oral tacrolimus (immunosuppressant) might lead to increased tacrolimus plasma levels.

Neo-Zol may reduce the effectiveness of some birth control methods, such as condoms, diaphragms, or vaginal spermicides. This effect is temporary and occurs only during treatment. Do not use tampons, intravaginal douches or other vaginal products while using this product.

Neo-Zol Vaginal Cream is for vaginal use only. Avoid contact with eyes; if this happens, rinse thoroughly with water.

Neo-Zol Vaginal Cream is for vaginal use or use on irritated vaginal area only. Neo-Zol used externally should not be used for vaginal itching due to causes other than a yeast infection.

If Neo-Zol is accidentally swallowed, contact your local emergency room or Poison Control Centre immediately.

Keep Neo-Zol and all other medications out of the reach of children.

Neo-Zol should not be used by girls less than 12 years of age unless advised by a physician.

If you have any questions about Neo-Zol or vaginal infections, contact your pharmacist or physician.

Medicinal Ingredient: Clotrimazole 1.0%

STORE AT ROOM TEMPERATURE BETWEEN 15°C AND 30°C.

Prestige Pharma Inc.
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H4B 1E8

INFORMATION FOR THE CONSUMER

EDUCATIONAL BROCHURE

NEO-ZOL VAGINAL CREAM 2%

Clotrimazole Vaginal Cream USP 2%

Antifungal

FOR THE TREATMENT OF VAGINAL YEAST INFECTIONS

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4. How do I use Neo-Zol Vaginal Cream 2%?

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Filling the Applicator:

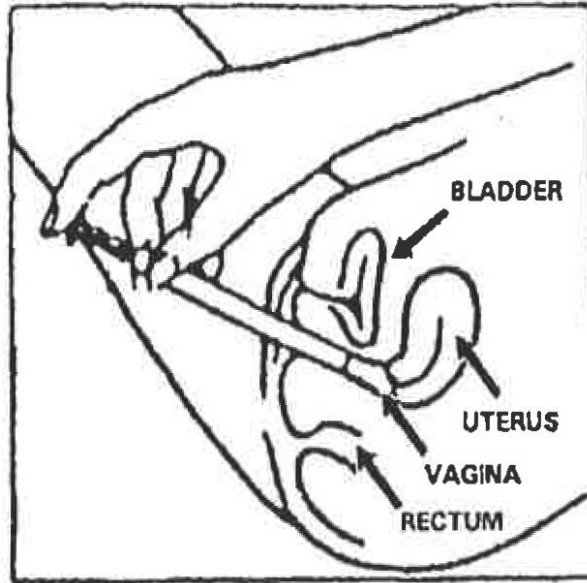
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Disposing of the Applicator:

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Medicinal Ingredient: Clotrimazole 2.0%

STORE AT ROOM TEMPERATURE BETWEEN 15°C AND 30°C.

Prestige Pharma Inc.
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MICROBIOLOGY

Clotrimazole is an antifungal agent with a broad spectrum of activity. In general, the in vitro activity of clotrimazole corresponds to that of tolnaftate, griseofulvin, and pyrrolnitrin against dermatophytes (*Trichophyton*, *Microsporum* and *Epidermophyton* species) and to that of the polyenes, amphotericin B and nystatin, against budding fungi (*Candida* and *Histoplasma* species).

In vitro, clotrimazole is fungistatic for most isolates of pathogenic fungi at concentrations of 0.02 to 10 µg/mL. The drug is fungicidal for many isolates of *Trichophyton*, *Microsporum*, *Epidermophyton* and *Candida* species at concentration of 0.1 to 2 µg/mL.

No one-step or multiple-step secondary resistance to clotrimazole has developed during successive passages of *C. albicans*, *C. krusei*, *C. pseudotropicalis*, *T. mentagrophytes*, *T. rubrum*, *Cryptococcus neoformans*, *Aspergillus niger*, and *A. nidulans*. Only a few isolates have been designated as having primary resistance to clotrimazole: a single isolate of *C. guilliermondii*, six isolates of *C. neoformans*, three isolates of *Paracoccidioides brasiliensis* and two isolates of *Blakeslea trispora*.

Topical application of clotrimazole has been effective in the treatment of skin infections experimentally induced in the guinea pig with *T. mentagrophytes* and *T. quinckeanum*. Clinical studies conducted as double-blind trials with mycological control have shown that clotrimazole is effective in the treatment of tinea cruris, tinea corporis, tinea pedis, tinea versicolor and cutaneous candidiasis. Mycological examinations have proven its efficacy against *Trichophyton rubrum*, *T. mentagrophytes*, *Malassezia furfur* and *Candida albicans*. Griseofulvin-resistant dermatophytes show no cross resistance to clotrimazole. It may be assumed, therefore, that the site of action of this drug is different from that of other antimycotics. Consequently, there is no cross resistance between these agents.

Antifungal Activity in Vitro

Minimum inhibitory concentrations (MICs) of clotrimazole were determined in serial dilution in broth or agar and in agar diffusion tests using the punched hole procedure. Conventional culture substrates, incubation times, and incubation temperatures were used. At concentrations less than 2 µg/mL, clotrimazole was fungicidal for many isolates of *C. albicans*, *Trichophyton* sp., *Microsporum* sp., and *Epidermophyton* sp., tested, and at concentrations less than 5 µg/mL, clotrimazole was fungistatic for other isolates of these species. Addition of bovine serum to the culture media at a final concentration of 30% resulted in somewhat higher MICs of clotrimazole.

The in vitro antifungal activity of clotrimazole was comparable to that of pyrrolnitrin; either compound at 0.78 µg/mL was fungicidal for most strains of *Trichophyton* sp., *Microsporum* sp. and *Epidermophyton* sp., tested.

The type of action of clotrimazole was determined in the Warburg apparatus by measuring the oxygen consumption of proliferating organisms exposed to varying concentrations of the drug. Additional studies were performed using a classical subculture technique with organism counts made after 16, 24 and 48 hours of exposure to the drug. These experiments showed that the primary action of clotrimazole at concentrations up to 20 µg/mL is fungistatic and affects only proliferating organisms. At concentrations greater than 20 µg/mL, clotrimazole was fungicidal for some organisms.

The determinations of MICs of clotrimazole for budding fungi and for biphasic fungi in the yeast phase have been shown to be dependent on the size of the inoculum and the length of incubation time. MICs for several isolates of *Candida albicans* and *Torulopsis glabrata* were higher when the inoculum size or incubation time or both were increased.

The effects of inoculum size has been attributed to binding of clotrimazole to the surface of the fungal cells. This was established in a study of turntable cultures of *C. albicans*. After 24 hours, the amount of clotrimazole in a nutrient substrate was reduced from 1 µg/mL to 0.7 µg/mL by an inoculum of 1 to 5 x 10⁵ cells/mL.

A larger inoculum, 1 x 10⁸ cells/mL, reduced the drug concentration from 1 µg/mL to 0.3 µg/mL. When the cultures were centrifuged and the cell sediment was washed with physiological saline solution, the wash solutions contained clotrimazole in concentrations of 0.2 µg/mL to 0.4 µg/mL.

The effect of incubation time on the determination of MIC values is thought to be related to the mechanism of action of clotrimazole. Initial studies indicated that clotrimazole acted as an antimetabolite upon the amino acid and protein metabolism of the fungi, causing a gradual inhibition of fungal growth.

However, recent studies using *C. albicans* as the test organism have shown that the primary mode of action of clotrimazole is damage to the permeability of the cell membrane. Exposure of *C. albicans* to clotrimazole caused leakage of intracellular phosphorus compounds into the ambient medium with a concomitant breakdown of cellular nucleic acids. The onset of these events was rapid and extensive after exposure of *C. albicans* to the drug and caused a time-dependent and concentration-dependent inhibition of fungal growth.

Resistance Development

Only a few isolates have been designated as having primary resistance to clotrimazole; a single isolate of *Candida guilliermondii*, six isolates of *Cryptococcus neoformans*, three isolates of *Paracoccidioides brasiliensis*, and two isolates of *Blakeslea trispora*. The potential for development of secondary resistance to clotrimazole was determined for several organisms by successive passages in a liquid medium, successive passages on a solid medium, or the Warburg proliferation test. Growth of dermatophytes and yeasts on Szybalski plates was also used as a method for determining the development of secondary resistance. No change in sensitivity was detected for *C. albicans* in any of the tests for secondary resistance, and no change in

sensitivity was detected for Trichophyton mentagrophytes, T. rubrum, C. krusei, C. pseudotropicalis, C. neoformans, Aspergillus niger, or A. nidulans after successive passages on liquid and solid media. Possible resistance development was noted in successive passages of Torulopsis glabrata and other Torulopsis species. Data obtained from Szybalski plate growth and from other tests indicated that dermatophytes and yeasts do not develop one-step or oligo-step secondary resistance.

PHARMACOLOGY

Pharmacokinetics

Metabolism studies performed after oral or intravenous administration have shown that in most species studied, levels of clotrimazole in tissue and serum are low. The majority of the drug is excreted as metabolites in the feces, with small amounts excreted in the urine. Human studies indicate slow excretion following oral administration of ¹⁴C-labelled clotrimazole (greater than 6 days). After intraperitoneal and subcutaneous administration, very low levels have been observed in the urine. The absorption and organ distribution of the drug is very poor when administered parenterally.

The pharmacokinetics of topically applied clotrimazole in human subjects have been evaluated by Duhm et al. who reported on the penetration of radioactive clotrimazole 1% cream and 1% solution into intact and acutely inflamed skin. Six hours after application of the drug, the concentration of clotrimazole found in skin layers varied from 100 µg/cm³ in the stratum corneum to 0.5 to 1.0 µg/cm³ in the stratum reticulare and <0.1 µg/cm³ in the subcutis. No measurable amount of radioactivity (0.001 µg/mL) was found in the serum within 48 hours after application of 0.5 mL of the solution or 0.8 g of the cream.

Intravaginal application of ¹⁴C-labelled clotrimazole inserts containing 100 mg of active substance in human subjects has shown that the amount absorbed is less than 1/200 of that absorbed after the oral administration of 1.5 g of clotrimazole. The maximum serum concentration values were between 0.016 and 0.05 µg/mL from one to three days after intravaginal application. Intravaginal application in human subjects of 5 mL ¹⁴C-labelled clotrimazole vaginal cream containing 50 mg of active substance has shown that the systemic absorption of clotrimazole from the Vaginal Cream is quantitatively proportional to that from the Vaginal Inserts.

In animal experiments, clotrimazole exerts an in vitro and in vivo, dose-dependent, stimulating effect on certain microsomal enzyme systems which is approximately equal to that of phenobarbital in its inductive potential. However, this stimulating effect subsides rapidly when treatment is discontinued. The enzyme-inductive effect of clotrimazole has been found to be intact in adrenalectomized animals.

In 8 double-blind studies and one single-blind study involving 432 patients using the 1% cream for 207 days, the average mycological cure rate was 72% with a range of 55 -90%. Oral contraceptives did not significantly alter mycological cure rates and overall success. In a limited

number of pregnant women, the 1 % cream appeared to be effective, although the cure rates seemed to be somewhat lower. In clinical trials with clotrimazole 2% vaginal cream, 266/303 patients (88%) had a negative culture for Candida sp. four weeks following treatment.

TOXICOLOGY

ACUTE TOXICITY (ORAL)

Animal

Species	LD ₅₀ mg/kg
Mouse	761 - 923
Rat	708 - 718
Rabbit	> 1000
Cat	kg > 1000; vomiting from 100 mg/kg
Dog	> 2000; vomiting from 100 mg/

Multidose Local Tolerance

1. Primary skin irritation (patch test): no detectable reddening on the intact rabbit skin at either 24 or 72 hours with 1 % solution or cream of clotrimazole. Very slight erythema formation after 24 hours in the scarified rabbit skin.
2. Primary irritation on conjunctival mucosa: clotrimazole solution or cream produced a transient conjunctival irritation in rabbits, consisting in low-grade reddening and a slight increase in secretion. No grossly detectable alterations were present in either the cornea or the iris of any of the treated animals. Both the cream and solution produced a transient, very slight reddening of the conjunctival mucosa. No alterations occurred on the cornea.
3. Subacute (up to 13 weeks) dermal tolerance: the application of 1% clotrimazole solution or 1% cream was systemically well tolerated; no edema was seen on the treated skin, although mild erythema was observed sporadically. The animals in all groups with abraded skin manifested a slight healing tendency. 21
4. Subacute (dogs: 14 days; monkeys: 13 weeks) local vaginal tolerance: the repeated application of clotrimazole vaginal inserts showed a satisfactory local and systemic tolerance. There were no detectable adverse effects, and the cytological examination in monkeys indicated variations consistent with normal estrus cycles.
5. Subacute (5 dogs: 30 days; 4 monkeys: 13 weeks; 10 healthy human volunteers: 28 days) local vaginal tolerance. The repeated application of Vaginal Cream showed a satisfactory local and systemic tolerance without adverse effects or abnormalities in vaginal cytology in all species.

REPRODUCTION AND TERATOLOGY

At dosages up to 100 mg/kg (subcutaneous), clotrimazole was well tolerated by pregnant mice, rats and rabbits, and it had no embryotoxic or teratogenic effect.

When given to pregnant rats at oral doses up to 100 mg/kg from day 6 through day 15 of gestation, the number of resorptions was higher and the fetal weights were lower than the controls, but the number of fetal malformations did not differ significantly from that of the control group.

Rats treated with clotrimazole for 10 weeks at dosage up to 50 mg/kg/day did not show any difference from the control group in the duration of estrus, fertility, duration of pregnancy, or in the number of implantations and resorptions. The dose of 50 mg/kg/day impaired the development of the young, and dams receiving this dose level raised fewer offspring.

The intravaginal administration of 100 mg/kg clotrimazole from the sixth to the fifteenth day of gestation was well tolerated by pregnant rats, and there were no harmful effects on the fertilization rate, the resorption rate, the mean fetal weight, and the frequency of stunted forms and of fetuses with slight bone alterations. No malformations were produced by this dose.

Human

In 453 cases under treatment which were evaluated with respect to photosensitivity and phototoxicity, no reactions were encountered.

Twenty normal subjects were tested in a controlled study for sensitivity to ultraviolet radiation. Areas of skin treated with clotrimazole were irradiated for 30 seconds on the first day, and for one-half minute longer each time on every second day thereafter. One of the 20 subjects was irradiated once only; 9 subjects three times, and 10 subjects four times. One subject developed papule formation after the first exposure to ultraviolet radiation.

There were undesirable effects in three (0.5%) of 653 patients treated with clotrimazole vaginal cream which were possibly related to treatment. Discontinuation of treatment was necessary in a patient with a sensation of vaginal burning and in another patient with a possible allergic reaction, manifested by vaginal burning, local irritation and erythema. Treatment was, however, continued in a patient with intercurrent cystitis.

REFERENCES

- 1) Cartwright, R.Y.: Clotrimazole in the Treatment of Acute and "Resistant" Vaginal Candidiasis. Postgrad. Med. J. 50, Suppl. 1, 90-92 (1974).
- 2) Duhm, B., Maul, W., and Medenwald, H., et al.: Pharmakokinetik nach topischer Anwendung von Bisphenyl-(2-chlorophenyl)-1-imidazolyl-methan (¹⁴C) after topical application). Arzneimittel-Forschung 22:1276-1280 (1972). English version, Drugs Made in Germany 15:99-103 (1972).
- 3) Dunster, G.D.: Vaginal candidiasis in pregnancy - A trial of clotrimazole. Postgrad. Med. J. 50, Suppl. 1, 86-88 (1974).
- 4) Fredriksson, T.: Topical treatment with BAY b 5097. A new broad spectrum antimycotic agent. Brit. J. of Dermatology 86:628-630 (1972).
- 5) Freis, A.: The tolerance of Clotrimazole on Topical Application. Drugs made in Germany XV. 120-121 (1972).
- 6) Higton, B.K.: A trial of clotrimazole and nystatin in vaginal candidiasis. Postgrad. Med. J. 50, Suppl. 1, 95-96 (1974).
- 7) Holt, R.: Studies on a broad-spectrum antimycotic agent FB b 5097. X. Int. Congress for Microbiology, Mexico City, August, 1970.
- 8) Legal, H.P.: The treatment of trichomonas and candida vaginitis with clotrimazole vaginal tablets. Postgrad. Med. J. 50, Suppl. 1, 81-83 (1974).
- 9) Lohmeyer, H.: Treatment of candidiasis and trichomoniasis of the female genital tract. Postgrad. Med. J. 50, Suppl. 1, 78-79 (1974).
- 10) Masterton, G., et al.: Six-day clotrimazole therapy in vaginal candidiasis. Curr. Med. Res. Opin., (1975), 3, 83.
- 11) Milsom, I. and Forssman, L.: Treatment of vaginal candidiasis with a single 500 mg clotrimazole pessary. Br. J. Ven. Dis. 2, 124-126 (1982).
- 12) Plempel, M., Bartmenn, K., Buchel, K.H., and Regel, E.: BAY b 5097, a New Orally Applicable Antifungal Substance with Broad-spectrum Activity. Antimicrobial Agents and Chemotherap. 271-274 (1969).
- 13) Ritzerfeld, W. and Venschott, M.L.: In vitro Untersuchungen mit dem Antimykotikum 23 Chlortritylimidazol. Int. J. Clin. Pharmacology, Therapy and Tox. 4, No. 2, 204-206 (1971).
- 14) Schnell, J.D.: The incidence of vaginal candida and trichomonas infections and treatment of trichomonas vaginitis with clotrimazole. Postgrad. Med. J., 50, Suppl. 1, 79-81 (1974).
- 15) Iwata, K., Yamaguchi, H., Hiratani, T.: Mode of Action of Clotrimazole. Sabouraudia 11:158-166 (1973).
- 16) Iwata, K., Kanda, Y., Yamaguchi, H. et al.: Electron microscopic studies on the mechanism of action of clotrimazole. Sabouraudia 11:205-209 (1973).