PRODUCT MONOGRAPH

CLOTRIMADERM

Clotrimazole

(Topical Cream USP 1%, and Topical Solution USP 1%)

Antifungal Agent

Taro Pharmaceuticals Inc.
130 East Drive
Brampton, Ontario
L6T 1C1

Date of Preparation:
October 20, 1997
Date of Revision:
January 2003

PRODUCT MONOGRAPH

CLOTRIMADERM

Clotrimazole

(Topical Cream USP 1% and Topical Solution USP 1%)

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

CLOTRIMADERM Topical Cream 1% and CLOTRIMADERM Topical Solution 1% are indicated for the topical treatment of the following dermal infections:

(1) Tinea pedis, tinea cruris, and tinea corporis due to Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum;

(2) Candidiasis due to Candida albicans;

(3) Tinea versicolor due to Malassezia furfur;

CONTRAINDICATIONS

Hypersensitivity to CLOTRIMADERM.

PRECAUTIONS

As with all topical agents, skin sensitization may result. Use of CLOTRIMADERM Topical Cream 1% and CLOTRIMADERM Topical Solution 1% should be discontinued should such reactions occur, and appropriate therapy instituted.

Although the topical application of clotrimazole has resulted in very low serum and tissue levels, the use of CLOTRIMADERM Topical Cream 1% and CLOTRIMADERM Topical Solution 1% by pregnant or lactating women is not recommended unless it is on the advice of a physician.

CLOTRIMADERM Topical Cream 1% and CLOTRIMADERM Topical Solution 1% are not suitable for treating fungal infections of the nail or scalp.

Occlusive dressings should not be applied over CLOTRIMADERM Topical Cream 1% and CLOTRIMADERM Topical Solution 1% unless directed by a physician.

CLOTRIMADERM Topical Cream 1% and CLOTRIMADERM Topical Solution 1% are not for ophthalmic use.

ADVERSE REACTIONS

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

Erythema, stinging, blistering, peeling, edema, pruritus, urticaria, and general irritation of the skin have been reported infrequently.

Out of a total of 184 patients treated with the 1% cream, irritation was reported in 12 and soreness in 1 patient; therapy was discontinued in 3 patients. In comparison, one case of increased inflammation and pruritus and 1 case of folliculitis was reported in the 54 patients treated with the vehicle control.

DOSAGE AND ADMINISTRATION

Skin Infections

CLOTRIMADERM Topical Cream 1% and CLOTRIMADERM Topical Solution 1%

ADULTS (for the treatment of jock itch, athlete's foot and ringworm): Thinly apply and gently massage sufficient CLOTRIMADERM into the affected and surrounding skin areas twice daily, in the morning and evening. For the treatment to be completely successful CLOTRIMADERM should be applied regularly and in sufficient quantities.

Clinical improvement with relief of pruritus, usually occurs within the first week of treatment. The

symptoms of jock itch and ringworm usually resolve within 2-4 weeks. Athlete's foot may require at least four (4) weeks. In mycoses of the foot, treatment should be continued - even when it has led to rapid subjective improvement - for about 2 weeks after all symptoms have disappeared so that relapses may be prevented. If the signs and symptoms of the infection have not been resolved after four weeks of treatment with CLOTRIMADERM, a physician should be consulted.

If a cure is not mycologically confirmed, treatment should, as a rule, be continued for 2 weeks after all clinical symptoms have disappeared. Candida infections are generally treated for only 2 weeks.

Added hygienic measures are of special importance in the management of the often refractory fungal diseases of the foot. After washing, the feet - particularly between the toes - should be dried thoroughly to avoid trapped moisture. Well-fitting, ventilated shoes and cotton or wool socks are recommended to ensure a successful treatment outcome and to help prevent a recurrence.

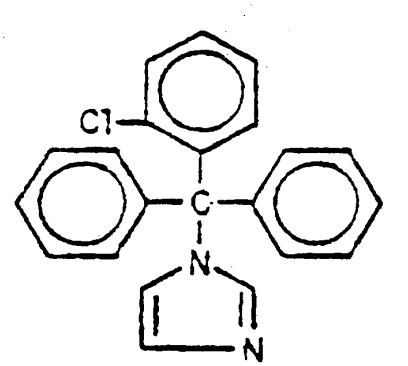
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: clotrimazole

Chemical Name: 1-(o-chloro-αα-diphenylbenzyl) imidazole

Structural Formula:



Molecular Formula: $C_{22}H_{17}ClN_2$ **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:
CLOTRIMADERM Topical Cream 1% contains 10 mg/g of clotrimazole in a cream base of sorbitan monostearate, polysorbate 60, cetyl esters wax, cetostearyl alcohol, 2-octyldodecanol and purified water with 1% benzyl alcohol as preservative.

CLOTRIMADERM Topical Solution 1% contains clotrimazole 10 mg/mL in polyethylene glycol 400.

STABILITY AND STORAGE RECOMMENDATIONS

Must be stored at room temperature between 15°C and 30°C.

AVAILABILITY OF DOSAGE FORM

CLOTRIMADERM Topical Cream 1% is supplied in 15 g, 30 g and 50 g tubes in cartons and in 500g jars.

CLOTRIMADERM Topical Solution 1% is available in 20 mL bottles.

INFORMATION FOR THE CONSUMER

CLOTRIMADERM

Clotrimazole Topical Cream USP 1% - Antifungal

Patient Information - Provided by the Physician or Pharmacist

FOR THE TREATMENT OF ATHLETE'S FOOT, JOCK ITCH,
RINGWORM, AND INFECTIONS OF THE SKIN
AND MUCOUS MEMBRANES

1. What is "athlete's foot"?

"Athlete's foot" is an infection of the foot caused by a fungus. It usually starts between the 3rd, 4th and 5th toes and later can spread to the skin under the toes. There may be itching and burning of the infected areas, and liquid may ooze out. If the toes are spread apart, the skin is usually found to be white, swollen and torn. If the infection spreads beyond the spaces between the toes to the area under the toes and the bottom of the foot, blisters and broken skin are the most common symptoms.

2. What is "jock itch"?

"Jock itch" is an infection in the groin area caused by a fungus. It occurs more commonly in males. The first signs of the infection are scaling of the skin, irritation and itching in the groin area. The scaling or rash may affect the upper thighs and sometimes the scrotum. Red, raised lesions may also be found on the scrotum and may extend to the anus.

3. What is "ringworm"?

"Ringworm" is a fungal infection of the skin, which may or may not be accompanied by symptoms. If symptoms are present, they usually involve scaling of the skin, crusting and the formation of pink to red lesions with clear centres. The lesions may appear circular with a clear area in the middle. The infection may occur anywhere on the body.

4. What is "tinea versicolor"?

This is a common fungal infection in young adults. The most noticeable symptom is patches of skin which are different in colour from the rest of the skin. These patches can be white, brown, or have no pigment. They are usually found on the chest, neck, abdomen, back and occasionally on the face. The skin in the affected areas may have scales, but these are not obvious unless the area is scratched. The condition is often noticed in the summer, because the white areas do not tan, but appear as white

"sun-spots" of different sizes. Itching is uncommon and occurs only when the person is hot and sweating.

5. What is "candidiasis"?

"Candidiasis" is a yeast infection of the skin and mucous membranes. It often appears in the armpits, creases of the neck, the groin, between the toes or buttocks, and beneath large breasts. The usual symptoms are burning, itching, cracks and scaling of the skin with small, red lesions.

6. How do I cure a fungal or yeast infection?

To cure an infection, it is necessary to kill the overgrowth of organisms that have caused the infection. CLOTRIMADERM Topical Cream 1% can cure most fungal or yeast infections such as athlete's foot, jock itch, ringworm, tinea versicolor and candidiasis. Even though the symptoms of your infection may be relieved in only a few days, you should use CLOTRIMADERM for the full treatment period. If your symptoms do not disappear or improve after 2 weeks of treatment (up to 4 weeks for athlete's foot), or if they get worse during treatment, discontinue treatment and contact your physician.

7. How do I use CLOTRIMADERM Topical Cream1%?

ADULTS (for the treatment of jock itch, athlete's foot and ringworm): Thinly apply and gently massage sufficient CLOTRIMADERM Topical Cream 1% into the affected and surrounding skin areas twice daily, in the morning and evening. Do not cover the medication with a bandage unless advised to do so by your physician. For the treatment to be completely successful, CLOTRIMADERM Topical Cream 1% should be applied regularly and in sufficient quantities. If you miss a dose, do not apply twice as much medication at the next dosing. "Athlete's foot" should be treated for 4 weeks, while "jock itch", "ringworm", "tinea versicolor", and "candidiasis" usually require 2 weeks of treatment.

8. How can I help prevent "athlete's foot"?

Bathe your feet regularly with soap and water. Towel-dry your feet, paying special attention to the area between the toes. Let your feet air-dry for 5 to 10 minutes. Wear absorbent socks made of 100% cotton or wool and well-fitting shoes that allow air circulation. Change your socks and shoes frequently. Avoid walking in bare feet at health clubs, public pools and other wet areas.

9. Important Warnings

Do not use CLOTRIMADERM 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 CLOTRIMADERM, discontinue use and contact your physician.

CLOTRIMADERM Topical Cream 1% is not suitable for treating fungal infections of the nail or scalp.

CLOTRIMADERM 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.

Occlusive dressings should not be applied on top of CLOTRIMADERM Topical Cream 1% unless directed by a physician.

CLOTRIMADERM Topical Cream 1% is for topical use only.

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

Keep CLOTRIMADERM and all other medications out of the reach of children.

Do not use on children under 2 years of age, unless recommended by a doctor.

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

If you have any questions about CLOTRIMADERM or topical fungal infections, contact your physician or pharmacist.

Medicinal Ingredient: Clotrimazole 1 %.

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

Taro Pharmaceuticals Inc., 130 East Drive, Brampton, Ontario L6T 1C1, Canada.

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. guillermondii, 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 10^5 cells/mL.

A larger inoculum, 1 x 10^8 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 guillermondii, 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 ^{14}C-labelled clotrimazole (greater than 6 days). After intraperitoneal and subcutaneous administration, very low levels have been observed in the urine. Sitka reported levels of about 1% of the quantity of clotrimazole in the 24-hour urine in newborns and premature infants. 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 $\mu g/cm^3$ in the stratum corneum to 0.5 to 1.0 $\mu g/cm^3$ in the stratum reticulare and < 0.1 $\mu g/cm^3$ 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. Sitka et al. reported serum levels of about 3 μg/mL in newborns and prematures and about 2.7 μg/mL in school children. Due to delayed excretion, prematures and newborns still showed values of 0.4 to 1.2 μg/mL after 24 hours; this level dropped faster to the zero point after 12 hours in older children.

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.

Results of twenty two mycologically controlled double-blind, one mycologically controlled single-blind, and four mycologically controlled open studies show that Clotrimazole 1% solution and cream are effective in the treatment of tinea cruris, tinea corporis, tinea pedis, tinea versicolor and cutaneous candidiasis. For the cream, mycological cure rates were 80% for tinea cruris/tinea corporis, 67% for tinea pedis, 88% for tinea versicolor and 92% for cutaneous candidiasis as compared to 4.7%, 0%, 37.5% and 0%, respectively, for the vehicle control (total of 238 patients).

TOXICOLOGY

ACUTE TOXICITY (ORAL)

Animal

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

Multidose Local Tolerance

1. Primary skin irritation (patch test): no detectable reddening on the intact rabbit skin at either 24 or 72 hours with Clotrimazole 1% solution or cream. Very slight erythema formation was observed 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 of 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.

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 doses 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 50mg/kg/day impaired the development of the young, and dams receiving this dose level raised fewer offspring.

Human

In 679 of 721 patients with dermatomycosis under treatment for several months, Clotrimazole 1% solution and cream were tolerated without difficulty. In 12 cases a low-grade irritation was observed during treatment which, however, necessitated neither the interruption of therapy nor the institution of any other therapeutic measures. In 17 cases poor tolerance was observed which resulted in interruption of the treatment. In 3 of these 17 patients an epicutaneous test with 1% solution was positive.

In 3 of 200 patients suffering mainly from allergy and eczemas, a positive epicutaneous test was obtained.

In 133 normal test subjects, 1% solution was examined in a continuous-exposure test lasting up from 14-25 days. No irritation was noted in any of these subjects.

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.

Allergies and skin irritations after application of Clotrimazole Topical Cream 1% could not be determined even after extensive testing as reported by Sitka et al. Also, they note that side effects are less pronounced in children than in adults. This is attributed to the observation that there is no interference by clotrimazole with hepatic enzymes in children as is evidenced in adults.

REFERENCES

1) Duhm B, Maul W, Medenwald H et al.: Pharmakokinetik nach topischer Anwendung von Bisphenyl-(2-chlorophenyl)-1-imidazolyl-methan-(^{14}C) after topical application). Arzneimittel- Forschung 1972;22:1276-1280. English version, Drugs Made in Germany 1972; 15:99-103.

2) Fredriksson T. Topical treatment with BAY b 5097. A new broad spectrum antimycotic agent. Brit. J. of Dermatology 1972; 866:628-30.

3) Freis A. The tolerance of Clotrimazole on Topical Application. Drugs made in Germany XV. 1972; 120-121.

4) Holt R. Studies on a broad-spectrum antimycotic agent FB b 5097. X. Int. Congress for Microbiology, Mexico City, August, 1970.

5) Plempel M, Bartmenn K, Buchel KH, Regel E. BAY b 5097, a New Orally Applicable Antifungal Substance with Broad-spectrum Activity. Antimicrobial Agents and Chemotherap.1969: 271 -4.

6) Sitka U, Weingartner L. Clotrimazole in the treatment of candida infections in hospital wards for premature and newborns children. Med Klin 1976;71 :635-9.

7) Waitz A, Weinstein M. Chemotherapeutic Evaluation of Clotrimazole (BAY b 5097), 1-(0-Chloro-a-a-Diphenylbenzyl) Imidazole). Appl. Microbiol. 1971;22(5) 891-8.

8) Iwata K, Yamaguchi H, Hiratani T. Mode of Action of Clotrimazole. Sabouraudia 1973;11:158-66.

9) Iwata K, Kanda Y, Yamaguchi H et al. Electron microscopic studies on the mechanism of action of Clotrimazole. Sabouraudia 1973;11:205-9.