PRODUCT MONOGRAPH

Clotrimazole Vaginal Cream USP 1%

Clotrimazole Vaginal Cream USP 2%

Clotrimazole External Cream
(Clotrimazole Vaginal Cream USP 1%)

Antifungal Agent

Taro Pharmaceuticals Inc.
130 East Drive
Brampton, Ontario
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Date of Revision:
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Control # 184799

PRODUCT MONOGRAPH

Clotrimazole Vaginal Cream USP 1%

Clotrimazole Vaginal Cream USP 2%

Clotrimazole External Cream
(Clotrimazole Vaginal Cream 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 eflux. 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

Clotrimazole Vaginal Cream 1% is indicated for the 6-day treatment of vaginal candidiasis.

Clotrimazole Vaginal Cream 2% is indicated for the 3-day treatment of vaginal candidiasis.

Clotrimazole External Cream (Clotrimazole Cream 1%) is indicated for the topical treatment of external irritation caused by vulvovaginal candidiasis.

CONTRAINDICATIONS

Hypersensitivity to Clotrimazole.

PRECAUTIONS

Clotrimazole Vaginal Cream and Clotrimazole External Cream are not for ophthalmic use.

Patients should seek medical advice if they have frequent vaginal infections or if their yeast infection returns in less than 2 months.

As with all topical agents, skin sensitization may result. Use of Clotrimazole 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.

While sexual relations may be had during treatment with Clotrimazole topical preparations, most couples wait until treatment has finished as the partner could become infected.

Concomitant medication with vaginal clotrimazole and oral tacrolimus/sirolimus (immunosuppressant) might lead to increased tacrolimus/sirolimus plasma levels. Patients should thus be thoroughly monitored for symptoms of tacrolimus/sirolimus overdosage.

Effects on Fertility
No human studies of the effects of clotrimazole on fertility have been performed; however, animal studies have not demonstrated any effects of the drug on fertility.

Use in Pregnancy
There are limited amounts of data from the use of clotrimazole in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see **REPRODUCTION AND TERATOLOGY**). Although intravaginal application of clotrimazole has shown negligible absorption from both normal and inflamed human vaginal mucosa, CLOTRIMADERM 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.

Use in Breastfeeding
Available pharmacodynamics/toxicological studies in animals have shown excretion of clotrimazole/metabolites in milk. Breastfeeding should be discontinued during treatment with

clotrimazole.

ADVERSE REACTIONS

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

For Clotrimazole External Cream

Immune system disorders: allergic reaction (syncope, hypotension, dyspnea, urticaria)

Skin and subcutaneous skin disorders: blisters, discomfort/pain, edema, erythema, irritation, peeling/exfoliation, pruritus, rash, stinging/burning.

For Clotrimazole Vaginal Cream
Immune system disorders: allergic reaction (syncope, hypotension, dyspnea, urticaria)

Reproductive system disorders and breast disorders: genital peeling, pruritus, edema, erythema, stinging, blistering, discomfort, general irritation of the skin and pelvic pain, vaginal hemorrhage

Gastrointestinal disorder: abdominal pain

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. Most adverse reactions involved local itching and burning. Only rarely was it necessary to discontinue treatment.

DOSAGE AND ADMINISTRATION

Vaginal Candidiasis

Clotrimazole Vaginal Cream 1%
The recommended daily dose is ONE full applicator intravaginally for SIX consecutive days, preferably at bedtime.

Clotrimazole Vaginal Cream 2%
The recommended daily dose is ONE full applicator intravaginally for THREE consecutive days, preferably at bedtime.

Clotrimazole External Cream
The cream should be spread onto the irritated area once or twice daily as needed, for up to seven consecutive days.

Vaginal Candidiasis may be accompanied by irritation in the vaginal area. Therefore, concomitant local treatment with Clotrimazole Vaginal Cream (or Clotrimazole External Cream) applied to the irritated vaginal area and as far as the anal region twice a day is advisable. Clotrimazole External Cream (or Clotrimazole Vaginal Cream) applied on the glans penis may prevent re-infection by the partner.

N.B.: The cream should be inserted deep intravaginally by means of the applicator (see **PRECAUTIONS**). 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.

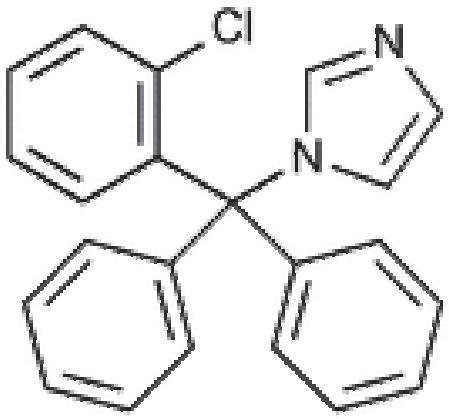
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: clotrimazole

Chemical Name: 1-(o-chloro-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

Clotrimazole 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.

Clotrimazole 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.

Clotrimazole External Cream 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.

STABILITY AND STORAGE RECOMMENDATIONS

Clotrimazole Vaginal Cream 1% and 2% and Clotrimazole External Cream must be stored at room temperature between 15°C and 30°C.

AVAILABILITY OF DOSAGE FORMS

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

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

INFORMATION FOR THE
CONSUMER EDUCATIONAL
BROCHURE

Clotrimazole vaginal cream USP 1% -
Antifungal

FOR THE TREATMENT OF VAGINAL YEAST
INFECTIONS READ THIS BEFORE USING

Taro Pharmaceuticals Inc.

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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, diarrhea, 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. Clotrimazole 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 Clotrimazole 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.

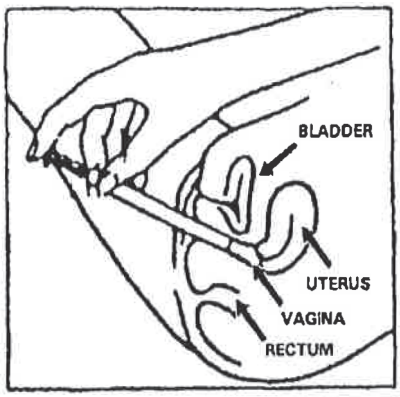
4. How do I use Clotrimazole Vaginal Cream 1%?

Clotrimazole Vaginal Cream 1% is used to treat vaginal yeast infections. Clotrimazole Vaginal Cream 1% 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. Clotrimazole Vaginal Cream 1% 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. The treatment should be finished before the onset of menstruation. While you may have sexual relations during treatment with Clotrimazole Vaginal Cream 1%, most couples wait until treatment has finished as your partner could become infected.

<u>Filling the Applicator:</u>
Remove the cap from the tube of Clotrimazole Vaginal Cream 1% 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 plunger stops, the proper amount of Clotrimazole Vaginal Cream 1% 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.

<u>Inserting the Medication:</u>
Clotrimazole 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 Clotrimazole Vaginal Cream 1% may be applied to the opening of the vagina to help provide extra relief.



Using the Cream Externally:
A small amount of Clotrimazole Vaginal Cream 1% maybe 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 Clotrimazole vaginal Cream 1% applicator is recyclable where facilities exist.

5. Important 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 Clotrimazole Vaginal Cream 1% 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 Clotrimazole Vaginal Cream 1% if you are pregnant, think you are, or are nursing, unless advised by a doctor.

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

Clotrimazole Vaginal Cream 1% 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.

Using vaginal Clotrimazole Vaginal Cream 1% and oral tacrolimus/sirolimus (immunosuppressant) might lead to increased tacrolimus/sirolimus plasma levels.

Clotrimazole Vaginal Cream 1% is for vaginal use only. Avoid contact with eyes; if this happens, rinse thoroughly with water. If Clotrimazole Vaginal Cream 1% is accidentally swallowed, contact your local emergency room or Poison Control Centre immediately. Keep Clotrimazole Vaginal Cream 1% and all other medications out of the reach of children.

Clotrimazole Vaginal Cream 1% should not be used by girls less than 12 years of age unless advised by a physician.

If you have any questions about Clotrimazole Vaginal Cream 1% or vaginal infections, contact your pharmacist or physician.

Medicinal Ingredient: Clotrimazole 1%
Non Medicinal ingredients: sorbitan monostearate, polysorbate 60, cetyl esters wax, cetostearyl alcohol, 2-octyl dodecanol, purified water, and benzyl alcohol 1% as preservative.

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

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

INFORMATION FOR THE
CONSUMER EDUCATIONAL
BROCHURE

Clotrimazole vaginal cream USP 2% -
Antifungal

FOR THE TREATMENT OF VAGINAL YEAST
INFECTIONS READ THIS BEFORE USING

Taro Pharmaceuticals Inc.

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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 oftheir 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, diarrhea, 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. Clotrimazole Vaginal Cream 2% 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 Clotrimazole Vaginal Cream 2% for a full 3 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.

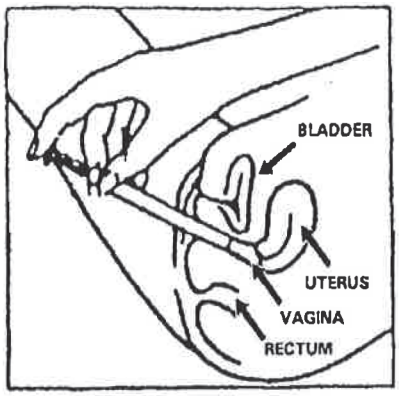
4. How do I use Clotrimazole Vaginal Cream 2%?

Clotrimazole Vaginal Cream 2% is used to treat vaginal yeast infections. Clotrimazole Vaginal Cream 2% s inserted high into the vagina once a day (preferably at bedtime) for 3 consecutive days. Sufficient cream is provided for 3 intravaginal applications. Extra cream is supplied for use in relieving the external itching and burning sometimes associated with a vaginal yeast infection. Clotrimazole Vaginal Cream 2% is only for use in the vagina and irritated vaginal area and should never be taken by mouth. The treatment should be finished before the onset of menstruation. While you may have sexual relations during treatment with Clotrimazole Vaginal Cream 2%, most couples wait until treatment has finished as your partner could become infected.

<u>Filling the Applicator:</u>
Remove the cap from the tube of Clotrimazole Vaginal Cream 2% 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 plunger stops, the proper amount of Clotrimazole Vaginal Cream 2% 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.

<u>Inserting the Medication:</u>
Clotrimazole Vaginal Cream 2% 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.



Disposing of the applicator
The Clotrimazole vaginal Cream 2% applicators are recyclable where facilities exist.

Using the cream externally:
A small additional amount of Clotrimazole Vaginal Cream 2% maybe 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.

5. Important 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 Clotrimazole Vaginal Cream 2% 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 Clotrimazole Vaginal Cream 2% if you are pregnant, think you are, or are nursing, unless advised by a doctor.

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

Clotrimazole Vaginal Cream 2% 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.

Using vaginal Clotrimazole and oral tacrolimus/sirolimus (immunosuppressant) might lead to increased tacrolimus/sirolimus plasma levels.

Clotrimazole Vaginal Cream 2% is for vaginal use only. Avoid contact with eyes; if this happens, rinse thoroughly with water. If Clotrimazole Vaginal Cream 2% is accidentally swallowed, contact your local emergency room or Poison Control Centre immediately. Keep Clotrimazole Vaginal Cream 2% and all other medications out of the reach of children.

Clotrimazole Vaginal Cream 2% should not be used by girls less than 12 years of age unless advised by a physician.

If you have any questions about Clotrimazole Vaginal Cream 2% or vaginal infections, contact your pharmacist or physician.

Medicinal Ingredient: Clotrimazole 2%

Non Medicinal Ingredients: sorbitan monostearate, polysorbate 60, cetyl esters wax, cetostearyl alcohol, 2-octyl dodecanol, purified water, and benzyl alcohol 1% as preservative.

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

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

INFO

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 orgamsms. 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 ofthe 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

Pharmacokinetics investigations after vaginal application have shown that only a small amount of clotrimazole (3-10%) is absorbed. Due to the rapid hepatic metabolization of absorbed clotrimazole into pharmacologically active metabolites, the resulting peak plasma concentrations of clotrimazole after vaginal application of a 500 mg dose were less than 10 ng/mL, suggesting that clotrimazole applied intravaginally is unlikely to lead to measurable systemic effects or side effects.

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. 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 $\mu g/mL$) 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 ^{14}C-labelled clotrimazole tablets 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 ^{14}C-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 Tablets.

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 7 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

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential. Effects in nonclinical studies, such as the effects on the liver (elevation of transaminases and alkaline phosphatase, liver cell hypertrophy) in the repeat-dose toxicity studies, the effects on the survival of the neonate in a fat fertility study, the species-specific indirect effects on the growth/survival of the fetus in a rat teratology study were observed with oral administration but only at exposures in excess of the maximum human exposure indicating little relevance to clinical use. Given the limited absorption of clotrimazole following a topic application, the potential for toxicity with the occasional use of clotrimazole 1% cream is further limited.

Carcinogenicity of clotrimazole was evaluated in a 78-week oral dosing study in rats and the results did not show any carcinogenic effect of clotrimazole.

Clotrimazole has been extensively studied in *in vitro* and *in vivo* mutagenicity assays, and no

evidence of genotoxic potential was found. In an Ames test, an *in vitro* biological assay to detect the mutagenicity of chemical compounds, clotrimazole showed no evidence of mutagenic activity. Clotrimaozle was found to be non-mutagenic in two additional *in vitro* studies, a gene mutation test in V79 cell lines and an Unscheduled DNA Synthesis (UDS) in primary rat hepatocytes. Studies evaluating the mutagenicity of clotrimazole in germ cells did not demonstrate mutagenic effects in a spermatogonia test in male hamsters, or in a dominant lethal test in male mice. Additionally, in mice, clotrimazole was not clastogenic in a micronucleus test.

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 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.

4. Subacute (dogs: 14 days; monkeys: 13 weeks) local vaginal tolerance: the repeated application of clotrimazole vaginal tablets 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.

Human

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

Twenty normal subjects were testing 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 ultra violet 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.

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.

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