

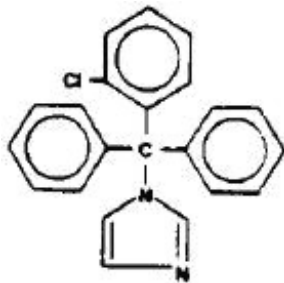
CLOTRIMAZOLE - clotrimazole cream
STAT RX USA LLC

For external use only

DESCRIPTION

Clotrimazole Cream USP, 1% contains clotrimazole, a synthetic antifungal agent having the chemical name {1-(o-Chloro- α , α -diphenylbenzyl)imidazole}; the molecular formula $C_{22}H_{17}ClN_2$; a molecular weight of 344.84; and the structural formula:

clotrimazole-01 STRUCTURE IMAGE



Clotrimazole is an odorless, white crystalline substance. It is practically insoluble in water, sparingly soluble in ether and very soluble in polyethylene glycol 400, ethanol and chloroform.

Each gram of Clotrimazole Cream contains 10 mg clotrimazole, dispersed in a vanishing cream base of sorbitan monostearate, polysorbate 60, cetyl esters wax, cetostearyl alcohol, 2-octyldodecanol, purified water, and benzyl alcohol (1%) as preservative.

CLINICAL PHARMACOLOGY

Clotrimazole is a broad-spectrum antifungal agent that is used for the treatment of dermal infections caused by various species of pathogenic dermatophytes, yeasts, and *Malassezia furfur*. The primary action of clotrimazole is against dividing and growing organisms.

In vitro, clotrimazole exhibits fungistatic and fungicidal activity against isolates of *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, *Microsporum canis* and *Candida* species including *Candida albicans*. In general, the *in vitro* activity of clotrimazole corresponds to that of tolnaftate and griseofulvin against the mycelia of dermatophytes (*Trichophyton*, *Microsporum*, and *Epidermophyton*), and to that of the polyenes (amphotericin B and nystatin) against budding fungi (*Candida*). Using an *in vivo* (mouse) and an *in vitro* (mouse kidney homogenate) testing system, clotrimazole and miconazole were equally effective in preventing the growth of the pseudomycelia and mycelia of *Candida albicans*.

Strains of fungi having a natural resistance to clotrimazole are rare. Only a single isolate of *Candida guilliermondi* has been reported to have primary resistance to clotrimazole.

No single-step or multiple-step resistance to clotrimazole has developed during successive passages of *Candida albicans* and *Trichophyton mentagrophytes*. No appreciable change in sensitivity was detected after successive passage of isolates of *C. albicans*, *C. krusei*, or *C. pseudotropicalis* in liquid or solid media containing clotrimazole. Also, resistance could not be developed in chemically induced mutant strains of polyene-resistant isolates of *C. albicans*. Slight, reversible resistance was noted in three isolates of *C. albicans* tested by one investigator. There is a single report that records the clinical emergence of *C. albicans* strain with considerable resistance to flucytosine and miconazole, and with cross-resistance to clotrimazole, the strain remained sensitive to nystatin and amphotericin B.

In studies of the mechanism of action, the minimum fungicidal concentration of clotrimazole caused leakage of intracellular phosphorus compounds into the ambient medium with concomitant breakdown of cellular nucleic acids and accelerated potassium efflux. Both these events began rapidly and extensively after addition of the drug.

Clotrimazole appears to be well absorbed in humans following oral administration and is eliminated mainly as inactive metabolites. Following topical and vaginal administration, however, clotrimazole appears to be minimally absorbed.

Six hours after the application of radioactive clotrimazole 1% cream and 1% solution onto intact and acutely inflamed skin, the concentration of clotrimazole varied from 100 mcg/cm³ in the stratum corneum to 0.5 to 1 mcg/cm³ in the stratum reticulare, and 0.1 mcg/cm³ in the subcutis. No measurable amount of radioactivity (≤ 0.001 mcg/mL) was found in the serum within 48 hours after application under occlusive dressing of 0.5 mL of the solution or 0.8 g of the cream. Only 0.5% or less of the applied radioactivity was excreted in the urine.

Following intravaginal administration of 100 mg ¹⁴C-clotrimazole vaginal tablets to nine adult females, an average peak serum level, corresponding to only 0.03 ug equivalents/mL of clotrimazole, was reached one to two days after application. After intravaginal administration of 5 g of 1% ¹⁴C-clotrimazole vaginal cream containing 50 mg active drug, to five subjects (one with candidal colpitis), serum levels corresponding to approximately 0.01 ug equivalents/mL were reached between 8 and 24 hours after application.

INDICATIONS AND USAGE

Clotrimazole Cream is indicated for the topical treatment of candidiasis due to *Candida albicans* and tinea versicolor due to *Malassezia furfur*.

Clotrimazole is also available as a nonprescription item which is indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Microsporum canis*.

CONTRAINDICATIONS

Clotrimazole Cream is contraindicated in individuals sensitive to its components.

WARNINGS AND PRECAUTIONS

WARNINGS

Clotrimazole Cream is not for ophthalmic use.

PRECAUTIONSGeneral

If irritation or sensitivity develops with the use of Clotrimazole Cream, treatment should be discontinued and appropriate therapy instituted.

Information for Patients

The patient should be advised to:

1. Use the medication for the full treatment time even though the symptoms may have improved. Notify the physician if there is no improvement after four weeks of treatment.
2. Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, oozing) indicative of possible sensitization.
3. Avoid the use of occlusive wrappings or dressings.
4. Avoid sources of infection or reinfection.

Laboratory Tests

If there is lack of response to Clotrimazole Cream, appropriate microbiological studies should be repeated to confirm the diagnosis and rule out other pathogens before instituting another course of antimycotic therapy.

Drug Interactions

Synergism or antagonism between clotrimazole and nystatin, or amphotericin B, or flucytosine against strains of *C. albicans* has not been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility

An 18-month oral dosing study with clotrimazole in rats has not revealed any carcinogenic effect.

In tests for mutagenesis, chromosomes of the spermatophores of Chinese hamsters which had been exposed to clotrimazole were examined for structural changes during the metaphase. Prior to testing, the hamsters had received five oral clotrimazole doses of 100 mg/kg body weight. The results of this study showed that clotrimazole had no mutagenic effect.

Usage in Pregnancy

Pregnancy Category B

The disposition of ¹⁴C-clotrimazole has been studied in humans and animals. Clotrimazole is very poorly absorbed following dermal application or intravaginal administration to humans. (See CLINICAL PHARMACOLOGY)

In clinical trials, use of vaginally applied clotrimazole in pregnant women in their second and third trimesters has not been associated with ill effects. There are, however, no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy.

Studies in pregnant rats with intravaginal doses up to 100 mg/kg have revealed no evidence of harm to the fetus due to clotrimazole.

High oral doses of clotrimazole in rats and mice ranging from 50 to 120 mg/kg resulted in embryotoxicity (possibly secondary to maternal toxicity), impairment of mating, decreased litter size and number of viable young and decreased pup survival to weaning. However, clotrimazole was not teratogenic in mice, rabbits and rats at oral doses up to 200, 180 and 100 mg/kg, respectively. Oral absorption in the rat amounts to approximately 90% of the administered dose.

Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly indicated during the first trimester of pregnancy.

Nursing Mothers

It is not known whether this drug is excreted in human milk, caution should be exercised when clotrimazole is used by a nursing woman.

Pediatric Use

Safety and effectiveness in children have been established for clotrimazole when used as indicated and in the recommended dosage.

ADVERSE REACTIONS

The following adverse reactions have been reported in connection with the use of this product: erythema, stinging, blistering, peeling, edema, pruritus, urticaria, burning, and general irritation of the skin.

OVERDOSAGE

Acute overdosage with topical application of clotrimazole is unlikely and would not be expected to lead to a life-threatening situation.

DOSAGE AND ADMINISTRATION

Gently massage sufficient Clotrimazole Cream into the affected and surrounding skin areas twice a day, in the morning and evening.

Clinical improvement, with relief of pruritus, usually occurs within the first week of treatment with Clotrimazole Cream. If the patient shows no clinical improvement after four weeks of treatment with Clotrimazole Cream, the diagnosis should be reviewed.

HOW SUPPLIED

Clotrimazole Cream USP, 1% is supplied in 15, 30, 45, and (2 × 45) gram tubes.

Store between 2°- 30°C (36°- 86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Mfd. by: **TARO Pharmaceuticals Inc.**, Bramalea, Ontario, Canada L6T 1C3

Revision Date: June, 1996

PACKAGE LABEL

CLOTRIMAZOLE 15GM LABEL IMAGE



CLOTRIMAZOLE

clotrimazole cream

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:16590-060(NDC:51672-1275)
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CLOTRIMAZOLE (UNII: G07GZ97H65) (CLOTRIMAZOLE - UNII:G07GZ97H65)	CLOTRIMAZOLE	10 mg in 1 g

Inactive Ingredients

Ingredient Name	Strength
SORBITAN MONOSTEARATE (UNII: NVZ4I0H58 X)	
POLYSORBATE 60 (UNII: CAL22UVI4M)	
CETYL ESTERS WAX (UNII: D072FFP9GU)	
CETOSTEARYL ALCOHOL (UNII: 2DMT128MIS)	
OCTYLDODECYL STEARATE (UNII: K6F16QGO28)	
WATER (UNII: 059QF0KO0R)	
BENZYL ALCOHOL (UNII: LKG8494WBH)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:16590-060-15	15 g in 1 TUBE		
2	NDC:16590-060-30	30 g in 1 TUBE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA072640	08/31/1993	

Labeler - STAT RX USA LLC (786036330)**Establishment**

Name	Address	ID/FEI	Business Operations
STAT RX USA LLC		786036330	repack, relabel

Revised: 8/2010

STAT RX USA LLC