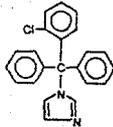


**PRODUCT INFORMATION**

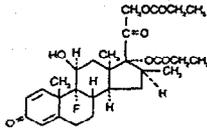
**LOTRISONE®**  
of clotrimazole and betamethasone dipropionate

**Cream, USP**  
For Dermatologic Use Only -  
Not for Ophthalmic Use

**DESCRIPTION** LOTRISONE Cream contains a combination of clotrimazole, USP, a synthetic antifungal agent, and betamethasone dipropionate, USP, a synthetic corticosteroid, for dermatologic use.  
Chemically, clotrimazole is 1-(*o*-Chloro- $\alpha,\alpha$ -diphenylbenzyl)imidazole, with the empirical formula  $C_{22}H_{17}ClN_2$ , a molecular weight of 344.8, and the following structural formula:



Clotrimazole is an odorless, white crystalline powder, insoluble in water and soluble in ethanol.  
Betamethasone dipropionate has the chemical name 9-Fluoro-11 $\beta$ , 17,21-trihydroxy-16 $\beta$ -methylpregna-1,4-diene-3,20-dione 17,21-dipropionate, with the empirical formula  $C_{28}H_{37}FO_7$ , a molecular weight of 504.6, and the following structural formula:



Betamethasone dipropionate is a white to creamy white, odorless crystalline powder, insoluble in water.  
Each gram of LOTRISONE Cream contains 10.0 mg clotrimazole, USP and 0.64 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in a hydrophilic emollient cream consisting of purified water, mineral oil, white petrolatum, cetearyl alcohol, ceteareth-30, propylene glycol, sodium phosphate monobasic, and phosphoric acid; benzyl alcohol as preservative.  
LOTRISONE is a smooth, uniform, white to off-white cream.

**CLINICAL PHARMACOLOGY**

**Clotrimazole**

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*, and *Microsporum canis*. In general, the *in vitro* activity of clotrimazole corresponds to that of tolnaftate and griseofulvin against the mycelia of dermatophytes (*Trichophyton*, *Microsporum*, and *Epidermophyton*).

*In vivo* studies in guinea pigs infected with *Trichophyton mentagrophytes* have shown no measurable loss ofazole activity due to combination with betamethasone dipropionate.

Strains of fungi having a natural resistance to clotrimazole have not been reported.  
Single-step or multiple-step resistance to clotrimazole has developed during successive passages of *Trichophyton mentagrophytes*.

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

Clotrimazole appears to be minimally absorbed following topical application to the skin. 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/cm<sup>2</sup> in the stratum corneum, to 0.5 to 1 mcg/cm<sup>2</sup> in the stratum reticulare, and 0.1 mcg/cm<sup>2</sup> 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.

**Betamethasone dipropionate**

Betamethasone dipropionate, a corticosteroid, is effective in the treatment of corticosteroid-responsive dermatoses primarily because of its anti-inflammatory, anti-pruritic, and vasoconstrictive actions. However, while the physiologic, pharmacologic, and clinical effects of corticosteroids are well known, the exact mechanisms of their actions in each disease are uncertain. Betamethasone dipropionate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

**Pharmacokinetics** The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. (See **DOSE AND ADMINISTRATION** section.)

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. (See **DOSE AND ADMINISTRATION** section.)

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

**Clotrimazole and betamethasone dipropionate**

In clinical studies of tinea corporis, tinea cruris, and tinea pedis, patients treated with LOTRISONE Cream showed a better clinical response at the first return visit than patients treated with clotrimazole cream. In tinea corporis and tinea cruris, the patient returned 3 days after starting treatment, and in tinea pedis, after 1 week. Mycological cure rates observed in patients treated with LOTRISONE Cream were as good as or better than those patients treated with clotrimazole cream.

In these same clinical studies, patients treated with LOTRISONE Cream showed statistically significantly better clinical responses and mycological cure rates when compared with patients treated with betamethasone dipropionate cream.

**INDICATIONS AND USAGE** LOTRISONE Cream 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** LOTRISONE Cream is contraindicated in patients who are sensitive to clotrimazole, betamethasone dipropionate, other corticosteroids or imidazoles, or to any ingredient in this preparation.

**PRECAUTIONS** **General** Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hypernatremia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. (See **DOSE AND ADMINISTRATION** section.)

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

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

**Information for Patients** Patients using LOTRISONE Cream should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. The medication is to be used for the full prescribed treatment time, even though the symptoms may have improved. Notify the physician if there is no improvement after 1 week of treatment for tinea cruris or tinea corporis, or after 2 weeks for tinea pedis.
3. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
4. The treated skin areas should not be bandaged or otherwise covered or wrapped as to be occluded. (See **DOSE AND ADMINISTRATION** section.)
5. When using this medication in the groin area, patients should be advised to use the medication for 2 weeks only, and to apply the cream sparingly. The physician should be notified if the condition persists after 2 weeks. Patients should also be advised to wear loose fitting clothing. (See **DOSE AND ADMINISTRATION** section.)
6. Patients should report any signs of local adverse reactions.
7. Patients should avoid sources of infection or reinfection.

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

The following tests may be helpful in evaluating HPA axis suppression due to the corticosteroid component:

- Urinary free cortisol test
- ACTH stimulation test

**Carcinogenesis, Mutagenesis, Impairment of Fertility** There are no animal or laboratory studies with the combination clotrimazole and betamethasone dipropionate to evaluate carcinogenesis, mutagenesis, or 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.

**Pregnancy Category C** There have been no teratogenic studies performed with the combination clotrimazole and betamethasone dipropionate.

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.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

There are no adequate and well-controlled studies in pregnant women on teratogenic effects from a topically applied combination of clotrimazole and betamethasone dipropionate. Therefore, LOTRISONE Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Drugs containing corticosteroids should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

**Nursing Mothers** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LOTRISONE Cream is used by a nursing woman.

**Pediatric Use** Safety and effectiveness in children below the age of 12 have not been established with LOTRISONE Cream.

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical dermatologics containing a corticosteroid to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

The use of LOTRISONE Cream in diaper dermatitis is not recommended.

**ADVERSE REACTIONS** The following adverse reactions have been reported in connection with the use of LOTRISONE Cream: paresthesia in 5 of 270 patients, maculopapular rash, edema, and secondary infection, each in 1 of 270 patients.

Adverse reactions reported with the use of clotrimazole are as follows: erythema, stinging, blistering, peeling, edema, pruritus, urticaria, and general irritation of the skin.

The following local adverse reactions are reported infrequently when topical corticosteroids are used as recommended. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

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

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See **PRECAUTIONS**.)

**DOSE AND ADMINISTRATION** Gently massage sufficient LOTRISONE Cream into the affected and surrounding skin areas twice a day, in the morning and evening, for 2 weeks in tinea cruris and tinea corporis and for 4 weeks in tinea pedis. The use of LOTRISONE Cream for longer than 4 weeks is not recommended.

Clinical improvement, with relief of erythema and pruritus, usually occurs within 3 to 5 days of treatment. If a patient with tinea cruris or tinea corporis shows no clinical improvement after 1 week of treatment with LOTRISONE Cream, the diagnosis should be reviewed. In tinea pedis, the treatment should be applied for 2 weeks prior to making that decision.

Treatment with LOTRISONE Cream should be discontinued if the condition persists after 2 weeks in tinea cruris and tinea corporis, and after 4 weeks in tinea pedis. Alternate therapy may then be instituted with LOTRIMIN Cream, a product containing an antifungal only.

LOTRISONE Cream should not be used with occlusive dressings.

**HOW SUPPLIED** LOTRISONE Cream is supplied in 15-gram (NDC 0085-0924-01) and 45-gram tubes (NDC 0085-0924-02); boxes of one.

Store between 2° and 30°C (36° and 86°F).



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