

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LOTRISONE cream safely and effectively. See full prescribing information for LOTRISONE cream.

LOTRISONE® (clotrimazole and betamethasone dipropionate) cream, 1%/0.05%, for topical use

Initial U.S. Approval: 1984

INDICATIONS AND USAGE

LOTRISONE cream contains a combination of clotrimazole, an azole antifungal, and betamethasone dipropionate, a corticosteroid, and is indicated for the topical treatment of symptomatic inflammatory tinea pedis, tinea cruris, and tinea corporis due to *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum* in patients 17 years and older. (1)

DOSAGE AND ADMINISTRATION

- Tinea pedis: Apply a thin film to the affected skin areas twice a day for 2 weeks. (2)
- Tinea cruris and tinea corporis: Apply a thin film to the affected skin area twice a day for 1 week. (2)
- LOTRISONE cream should not be used longer than 2 weeks in the treatment of tinea corporis or tinea cruris, and longer than 4 weeks in the treatment of tinea pedis. (2)
- Do not use with occlusive dressings unless directed by a physician. (2)
- Not for ophthalmic, oral or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Cream, 1%/0.05% (3)

Each gram of LOTRISONE cream contains 10 mg of clotrimazole and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- LOTRISONE cream can cause reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency during and after withdrawal of the treatment. Risk factor(s) are: use of high-potency topical corticosteroid, use over a large surface area or to areas under occlusion, prolonged use, altered skin barrier, liver failure, and young age. Modify use should HPA axis suppression develop. (5.1, 8.4)
- Pediatric patients may be more susceptible to systemic toxicity. (5.1, 8.4)
- The use of LOTRISONE cream in the treatment of diaper dermatitis is not recommended. (5.2)

ADVERSE REACTIONS

Most common adverse reactions reported for LOTRISONE cream were paraesthesia in 1.9% of patients and rash, edema, and secondary infections each in less than 1% of patients. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LOTRISONE cream is a combination of an azole antifungal and corticosteroid and is indicated for the topical treatment of symptomatic inflammatory tinea pedis, tinea cruris, and tinea corporis due to *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum* in patients 17 years and older.

2 DOSAGE AND ADMINISTRATION

Treatment of tinea corporis or tinea cruris:

- Apply a thin film of LOTRISONE cream into the affected skin areas twice a day for one week.
- Do not use more than 45 grams per week. Do not use with occlusive dressings.
- If a patient shows no clinical improvement after 1 week of treatment with LOTRISONE cream, the diagnosis should be reviewed.
- Do not use longer than 2 weeks.

Treatment of tinea pedis:

- Gently massage a sufficient amount of LOTRISONE cream into the affected skin areas twice a day for two weeks.
- Do not use more than 45 grams per week. Do not use with occlusive dressings.
- If a patient shows no clinical improvement after 2 weeks of treatment with LOTRISONE cream, the diagnosis should be reviewed.
- Do not use longer than 4 weeks.

LOTRISONE cream is for topical use only. It is not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Cream, 1%/0.05%. Each gram of LOTRISONE cream contains 10 mg of clotrimazole and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in a white to off-white cream base.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Effects on Endocrine System

LOTRISONE cream can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during treatment or after withdrawal of treatment. Cushing's syndrome and hyperglycemia may also occur due to the systemic effect of corticosteroids while on treatment. Factors that predispose a patient to HPA axis suppression include the use of high-potency steroids, large treatment surface areas, prolonged use, use of occlusive dressing, altered skin barrier, liver failure, and young age.

Because of the potential for systemic corticosteroid effects, patients may need to be periodically evaluated for HPA axis suppression. This may be done by using the adrenocorticotrophic hormone (ACTH) stimulation test.

In a small trial, LOTRISONE cream was applied using large dosages, 7 g daily for 14 days (BID) to the crural area of normal adult subjects. Three of the 8 normal subjects on whom LOTRISONE cream was applied exhibited low morning plasma cortisol levels during treatment. One of these subjects had an abnormal cosyntropin test. The effect on morning plasma cortisol was transient and subjects recovered 1 week after discontinuing dosing. In addition, 2 separate trials in pediatric subjects demonstrated adrenal suppression as determined by cosyntropin testing [see *Use in Specific Populations* (8.4)].

If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent corticosteroid.

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin-surface-to-body mass ratios [see *Use in Specific Populations* (8.4)].

5.2 Diaper Dermatitis

The use of LOTRISONE cream in the treatment of diaper dermatitis is not recommended.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials common adverse reaction reported for LOTRISONE cream was paresthesia in 1.9% of patients. Adverse reactions reported at a frequency < 1% included rash, edema, and secondary infection.

6.2 Postmarketing Experience

Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following local adverse reactions have been reported with topical corticosteroids: itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, skin atrophy, striae, miliaria, capillary fragility (ecchymoses), telangiectasia, and sensitization (local reactions upon repeated application of product).

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects,

Pregnancy Category C

There are no adequate and well-controlled studies with LOTRISONE cream in pregnant women. Therefore, LOTRISONE cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There have been no teratogenic studies performed in animals or humans with the combination of clotrimazole and betamethasone dipropionate. Corticosteroids are generally teratogenic in laboratory animals when administered at relatively low dosage levels.

Studies in pregnant rats with intravaginal doses up to 100 mg/kg (15 times the maximum human dose) revealed no evidence of fetotoxicity due to clotrimazole exposure.

No increase in fetal malformations was noted in pregnant rats receiving oral (gastric tube) clotrimazole doses up to 100 mg/kg/day during gestation Days 6 to 15. However, clotrimazole dosed at 100 mg/kg/day was embryotoxic (increased resorptions), fetotoxic (reduced fetal weights), and maternally toxic (reduced body weight gain) to rats. Clotrimazole dosed at 200 mg/kg/day (30 times the maximum human dose) was maternally lethal, and therefore, fetuses were not evaluated in this group. Also in this study, doses up to 50 mg/kg/day (8 times the maximum human dose) had no adverse effects on dams or fetuses. However, in the combined fertility, teratogenicity, and postnatal development study described above, 50 mg/kg clotrimazole was associated with reduced maternal weight gain and reduced numbers of offspring reared to 4 weeks.

Oral clotrimazole doses of 25, 50, 100, and 200 mg/kg/day (2-15 times the maximum human dose) were not teratogenic in mice. No evidence of maternal toxicity or embryotoxicity was seen in pregnant rabbits dosed orally with 60, 120, or 180 mg/kg/day (18-55 times the maximum human dose).

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. This dose is approximately one-fifth the maximum human dose. The abnormalities observed included umbilical hernias, cephalocele, and cleft palates.

Betamethasone dipropionate has not been tested for teratogenic potential by the dermal route of administration. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

8.3 Nursing Mothers

Systemically administered corticosteroids appear in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids can result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when LOTRISONE cream is administered to a nursing woman.

8.4 Pediatric Use

The use of LOTRISONE cream in patients under 17 years of age is not recommended.

Adverse events consistent with corticosteroid use have been observed in pediatric patients treated with LOTRISONE cream. In open-label trials, 17 of 43 (39.5%) evaluable pediatric subjects (aged 12-16 years old) using LOTRISONE cream for treatment of tinea pedis demonstrated adrenal suppression as determined by cosyntropin testing. In another open-label trial, 8 of 17 (47.1%) evaluable pediatric subjects (aged 12-16 years old) using LOTRISONE cream for treatment of tinea cruris demonstrated adrenal suppression as determined by cosyntropin testing.

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are, therefore also at greater risk of adrenal

insufficiency during and/or after withdrawal of treatment. Pediatric patients may be more susceptible than adults to skin atrophy, including striae, when they are treated with topical corticosteroids.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids [see *Warnings and Precautions* (5.1)].

Avoid use of LOTRISONE cream in the treatment of diaper dermatitis.

8.5 Geriatric Use

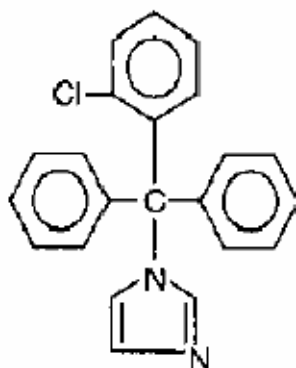
Clinical studies of LOTRISONE cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, greater sensitivity of some older individuals cannot be ruled out. The use of LOTRISONE cream under occlusion, such as in diaper dermatitis, is not recommended.

Postmarket adverse event reporting for LOTRISONE cream in patients aged 65 and above includes reports of skin atrophy and rare reports of skin ulceration. Caution should be exercised with the use of these corticosteroid-containing topical products on thinning skin.

11 DESCRIPTION

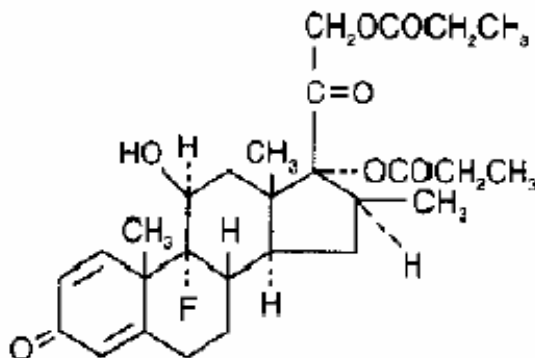
LOTRISONE (clotrimazole and betamethasone dipropionate) cream, 1%/0.05%, contains combinations of clotrimazole, an azole antifungal, and betamethasone dipropionate, a corticosteroid, for topical use.

Chemically, clotrimazole is 1-(o-chloro- α,α -diphenylbenzyl) imidazole, with the empirical formula $C_{22}H_{17}ClN_2$, a molecular weight of 344.84, and the following structural formula:



Clotrimazole is an odorless, white crystalline powder, insoluble in water and soluble in ethanol.

Betamethasone dipropionate has 9-fluoro-11 β ,17,21-trihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 17,21-dipropionate, with the empirical formula $C_{28}H_{37}FO_7$, a molecular weight of 504.59, 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 mg clotrimazole and 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone), in a white to off-white, hydrophilic cream consisting of benzyl alcohol as a preservative, cetareth-30, cetyl alcohol plus stearyl alcohol, mineral oil, phosphoric acid, propylene glycol, purified water, sodium phosphate monobasic monohydrate, and white petrolatum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Clotrimazole is an azole antifungal [see *Clinical Pharmacology* (12.4)].

Betamethasone dipropionate is a corticosteroid. Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action for the treatment of tinea pedis, tinea cruris and tinea corporis is unknown.

12.2 Pharmacodynamics

Vasoconstrictor Assay:

Studies performed with LOTRISONE cream indicate that these topical combination antifungal/corticosteroids may have vasoconstrictor potencies in a range that is comparable to high-potency topical corticosteroids. However, similar blanching scores do not necessarily imply therapeutic equivalence.

12.3 Pharmacokinetics

Skin penetration and systemic absorption of clotrimazole and betamethasone dipropionate following topical application of LOTRISONE cream has not been studied.

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. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption of topical corticosteroids. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids [see *Dosage and Administration* (2)].

Once absorbed through the skin, the pharmacokinetics of topical corticosteroids are 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.

12.4 Microbiology

Mechanism of Action:

Clotrimazole, an azole antifungal agent, inhibits 14- α -demethylation of lanosterol in fungi by binding to one of the cytochrome P-450 enzymes. This leads to the accumulation of 14- α -methylsterols and reduced concentrations of ergosterol, a sterol essential for a normal fungal cytoplasmic membrane. The methylsterols may affect the electron transport system, thereby inhibiting growth of fungi.

Activity In Vitro and In Vivo:

Clotrimazole has been shown to be active against most strains of the following dermatophytes, both in vitro and in clinical infections, *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum* [see *Indications and Usage* (1)].

Drug Resistance:

Strains of dermatophytes having a natural resistance to clotrimazole have not been reported. Resistance to azoles, including clotrimazole, has been reported in some *Candida* species.

No single-step or multiple-step resistance to clotrimazole has developed during successive passages of *Trichophyton mentagrophytes*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no adequate laboratory animal studies with either the combination of clotrimazole and betamethasone dipropionate or with either component individually to evaluate carcinogenesis.

Betamethasone was negative in the bacterial mutagenicity assay (*Salmonella typhimurium* and *Escherichia coli*) and in the mammalian cell mutagenicity assay (CHO/HGPRT). It was positive in the *in vitro* human lymphocyte chromosome aberration assay, and equivocal in the *in vivo* mouse bone marrow micronucleus assay.

Reproductive studies with betamethasone dipropionate carried out in rabbits at doses of 1.0 mg/kg by the intramuscular route and in mice up to 33 mg/kg by the intramuscular route indicated no impairment of fertility except for dose-related increases in fetal resorption rates in both species. These doses are approximately 5- and 38-fold the maximum human dose based on body surface areas, respectively.

In a combined study of the effects of clotrimazole on fertility, teratogenicity, and postnatal development, male and female rats were dosed orally (diet admixture) with levels of 5, 10, 25, or 50 mg/kg/day (approximately 1-8 times the maximum dose in a 60-kg adult based on body surface area) from 10 weeks prior to mating until 4 weeks postpartum. No adverse effects on the duration of estrous cycle, fertility, or duration of pregnancy were noted.

14 CLINICAL STUDIES

In clinical trials of tinea corporis, tinea cruris, and tinea pedis, subjects treated with LOTRISONE cream showed a better clinical response at the first return visit than subjects treated with clotrimazole cream. In tinea corporis and tinea cruris, the subject returned 3 to 5 days after starting treatment, and in tinea pedis, after 1 week. Mycological cure rates observed in subjects treated with LOTRISONE cream were as good as, or better than, in those subjects treated with clotrimazole cream. In these same clinical studies, patients treated with LOTRISONE cream showed better clinical responses and mycological cure rates when compared with subjects treated with betamethasone dipropionate cream.

16 HOW SUPPLIED/STORAGE AND HANDLING

LOTRISONE cream is white to off-white and supplied in 15-gram (NDC 0085-0924-01) and 45-gram tubes (NDC 0085-0924-02), boxes of one. Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Rx only

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information)

Inform the patient of the following:

- Use LOTRISONE cream as directed by the physician. It is for external use only.
- Avoid contact with the eyes, the mouth, or intravaginally.
- Do not use LOTRISONE cream on the face or underarms.
- Do not use more than 45 grams of LOTRISONE cream per week.
- When using LOTRISONE cream in the groin area, patients should use the medication for 2 weeks only, and apply the cream sparingly. Patients should wear loose-fitting clothing. Notify the physician if the condition persists after 2 weeks.
- Do not use LOTRISONE cream for any disorder other than that for which it was prescribed.
- Do not bandage, cover or wrap the treatment area unless directed by the physician. Avoid use of LOTRISONE cream in the diaper area, as diapers or plastic pants may constitute occlusive dressing.
- Report any signs of local adverse reactions to the physician. Advise patients that local reactions and skin atrophy are more likely to occur with occlusive use or prolonged use.
- This 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.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

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