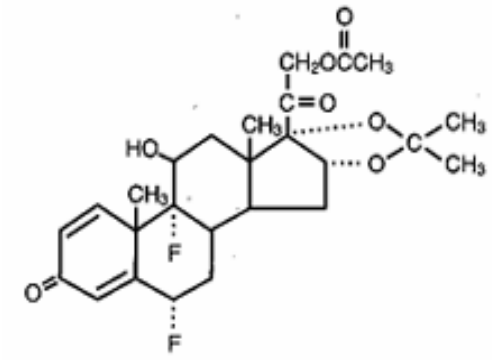
VANOS (fluocinonide) Cream, 0.1%
Rx Only

FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE

DESCRIPTION

VANOS (fluocinonide) Cream, 0.1% contains fluocinonide, a synthetic corticosteroid for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents. Fluocinonide has the chemical name 6 alpha, 9 alpha-difluoro-11 beta, 21-dihydroxy-16 alpha, 17 alpha-isopropylidenedioxypregna-1, 4-diene-3,20-dione 21-acetate. Its chemical formula is $C_{26}H_{32}F_2O_7$ and it has a molecular weight of 494.58.

It has the following chemical structure:



Fluocinonide is an almost odorless white to creamy white crystalline powder. It is practically insoluble in water and slightly soluble in ethanol.

Each gram of VANOS Cream contains 1 mg micronized fluocinonide in a cream base of propylene glycol USP, dimethyl isosorbide, glyceryl stearate (and) PEG-100 stearate, glyceryl monostearate NF, purified water USP, carbopol 980 NF, diisopropanolamine, and citric acid USP.

CLINICAL PHARMACOLOGY

The exact mechanism of action of topical corticosteroids, such as fluocinonide, in the treatment of psoriasis is not known. However, topical corticosteroids are thought to be effective primarily because of their anti-inflammatory, anti-pruritic, and vasoconstrictive

actions. The mechanism of the anti-inflammatory activity of topical corticosteroids, in general, is unclear. However, corticosteroids are thought to act by induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachadonic acid. Arachadonic acid is released from membrane phospholipids by phospholipase A_2.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusive dressings with hydrocortisone for up to 24 hours have not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Vasoconstrictor studies performed with VANOS Cream, 0.1% in healthy subjects indicate that it is in the super-high range of potency as compared with other topical corticosteroids; however, similar blanching scores do not necessarily imply therapeutic equivalence.

Application of VANOS Cream, 0.1% twice daily for 14 days in 18 adult patients with plaque-type psoriasis (10-50% BSA, mean 19.6% BSA) showed demonstrable HPA axis suppression in 2 patients (with 12% and 25% BSA) where the criterion for HPA axis suppression is a serum cortisol level of less than or equal to 18 micrograms per deciliter 30 minutes after stimulation with cosyntropin ($ACTH_{1-24}$).

Treatment of patients with VANOS Cream for more than 2 weeks at a time is not recommended, and only small areas should be treated at any one time due to the increased risk of HPA-axis suppression (See **PRECAUTIONS**).

HPA axis suppression has not been evaluated in psoriasis patients who are less than 18 years of age.

CLINICAL STUDIES

A double masked, vehicle controlled, randomized study of VANOS Cream was conducted in patients with plaque-type psoriasis. Patients with 2% to 10% body surface area involvement at baseline applied either VANOS Cream or Vehicle Cream to all affected areas either once daily (*qd*) or twice daily (*bid*) for 14 consecutive days. The primary measure of efficacy was the proportion of patients whose psoriasis lesions cleared or almost cleared at the end of treatment. The results are presented in the table below as patients cleared or almost cleared at Week 2 with once or twice daily application of VANOS Cream.

	VANOS Cream, *once daily* (n = 107)	Vehicle, *once daily* (n = 54)	VANOS Cream, *twice daily* (n = 107)	Vehicle, *twice daily* (n = 55)
Patients cleared	0 (0)	0 (0)	6 (6%)	0 (0)
Patients achieving treatment success*	19 (18%)	4 (7%)	33 (31%)	3 (6%)

*cleared or almost cleared

No efficacy studies have been conducted to compare VANOS (fluocinonide) Cream, 0.1% with any other topical corticosteroid product, including fluocinonide cream 0.05%.

INDICATIONS AND USAGE

VANOS (fluocinonide) Cream, 0.1%, is a corticosteroid indicated for treatment of plaque-type psoriasis affecting up to 10% body surface area (BSA). Use in patients under 18 years of age is not recommended because safety has not been established (see PRECAUTIONS: Pediatric Use section).

Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 60 g/week because the safety of VANOS Cream for longer than 2 weeks has not been established and because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Therapy should be discontinued when control of psoriasis has been achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

CONTRAINDICATIONS

VANOS Cream is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

General: Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment. Use of more than one corticosteroid-containing product at the same time may increase total systemic glucocorticoid exposure.

Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA-axis suppression. This may be done by using cosyntropin ($ACTH_{1-24}$) stimulation testing. Patients should not be treated

with VANOS Cream for more than 2 weeks at a time, and only small areas should be treated at any one time due to the increased risk of HPA-axis suppression.

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 corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Application of VANOS Cream, 0.1% twice daily for 14 days in 18 adult patients with plaque-type psoriasis (10-50% BSA, mean 19.6% BSA) showed demonstrable HPA axis suppression in 2 patients (11%).

HPA axis suppression has not been evaluated in psoriasis patients who are less than 18 years old. Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. (See **PRECAUTIONS – Pediatric Use.)**

If irritation develops, VANOS Cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of VANOS Cream should be discontinued until the infection has been adequately controlled.

VANOS Cream should not be used in the treatment of rosacea or perioral dermatitis, and should not be used on the face, groin, or axillae.

Information for the Patient: Patients using VANOS Cream should receive the following information and instructions. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or unintended effects:

1. VANOS Cream is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. VANOS Cream should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped, so as to be occlusive unless directed by the physician.

4. Patients should report to their physician any signs of local adverse reactions.
5. Other corticosteroid-containing products should not be used with VANOS Cream without first talking to the physician.
6. If no improvement is seen in 2 weeks, the patient should be instructed to contact a physician. The safety of the use of VANOS Cream for longer than 2 weeks has not been established.

Laboratory Tests: The cosyntropin ($ACTH_{1-24}$) stimulation test may be helpful in evaluating patients for HPA axis suppression.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of fluocinonide.

Fluocinonide revealed no evidence of mutagenic or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames test and an *in vitro* chromosomal aberration assay in human lymphocytes). However, fluocinonide was positive for clastogenic potential when tested in the in vivo mouse micronucleus assay.

Pregnancy Category C: Teratogenic Effects: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

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

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Use in patients under 18 years of age is not recommended. Safety and effectiveness in pediatric patients have not been established. 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 and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

HPA-axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to cosyntropin ($ACTH_{1-24}$) stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Geriatric Use: Clinical studies of VANOS Cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious.

ADVERSE REACTIONS

In clinical trials, a total of 443 patients with atopic dermatitis or plaque-type psoriasis were treated once daily or twice daily with VANOS Cream for 2 weeks. The most commonly observed adverse events in these clinical trials were as follows:

Adverse Event	VANOS Cream, *once daily* (n=216)	VANOS Cream, *twice daily* (n=227)	Vehicle Cream, *once or twice daily* (n=211)
Headache	8/216 (3.7%)	9/227 (4.0%)	6/211 (2.8%)
Application Site Burning	5/216 (2.3%)	4/227 (1.8%)	14/211 (6.6%)
Nasopharyngitis	2/216 (0.9%)	3/227 (1.3%)	3/211 (1.4%)
Nasal Congestion	3/216 (1.4%)	1/227 (0.4%)	0
Unspecified Application Site Reaction	1/216 (0.4%)	1/227 (0.4%)	3/211 (1.4%)

No other adverse events were reported by more than 1 subject receiving active treatment. The incidence of all adverse events was similar between the active treatment groups and the vehicle control groups.

The following additional local adverse reactions have been reported with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. 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.

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

OVERDOSAGE

Topically applied VANOS Cream can be absorbed in sufficient amounts to produce systemic effects (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Apply a thin layer of VANOS Cream once or twice daily to the affected skin areas, as directed by your physician. Twice daily application has been shown to be more effective in achieving treatment success after 2 weeks of treatment (see **CLINICAL STUDIES**).

Treatment with VANOS Cream should be limited to 2 consecutive weeks, and amounts greater than 60 g/week should not be used.

Therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

HOW SUPPLIED

VANOS (fluocinonide) Cream 0.1% is supplied in aluminum tubes as follows:

30 g (NDC 99207-523-30)
60 g (NDC 99207-525-60)

Store at controlled room temperature: 15° to 30°C (59° to 86°F).

Manufactured for:
MEDICIS, The Dermatology Company ®
Scottsdale, AZ 85258

Manufactured by:
Patheon, Inc.
Mississauga, Ontario
Canada L5N 7K9

Made in Canada

U.S. Patent 6,765,001

Prescribing information as of February, 2005.

PMS 151 | PMS 185 | PMS 293 | PMS 431

ULIDEX CREAM 0.1% 1.5g CARTON
8/30/04

NDC 99207-525-02

Vanos™
(fluocinonide) cream 0.1%

Sample—Not for Sale
Available in 30 and 60 g tubes

FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE

Rx only

MEDICIS
The Dermatology Company®

Dosage: See package insert for dosage information.

Manufactured for: MEDICIS,
The Dermatology Company
Scottsdale, AZ 85258
by: Patheon, Inc.
Mississauga, Ontario
Canada L5N 7K9
Made in Canada

U.S. Patent 6,765,001

NDC 99207-525-02

Vanos™
(fluocinonide) cream 0.1%

Sample—Not for Sale
Available in 30 and 60 g tubes

FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE

Rx only

Contains 20 sample tubes. Each tube contains 1.5 g.

MEDICIS
The Dermatology Company®

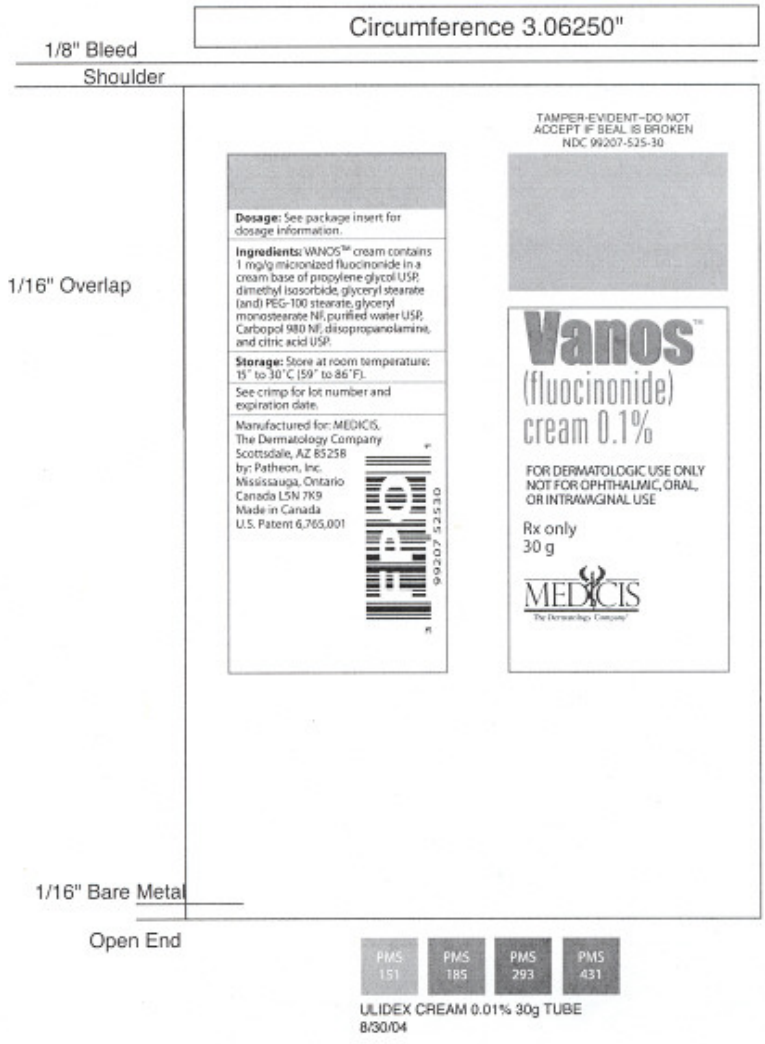
Ingredients: VANOS™ cream contains 1 mg/g micronized fluocinonide in a cream base of propylene glycol USP, dimethyl isosorbide, glyceryl stearate (and) PEG-100 stearate, glyceryl monostearate NF, purified water USP, Carbopol 980 NF, diisopropanolamine, and citric acid USP.

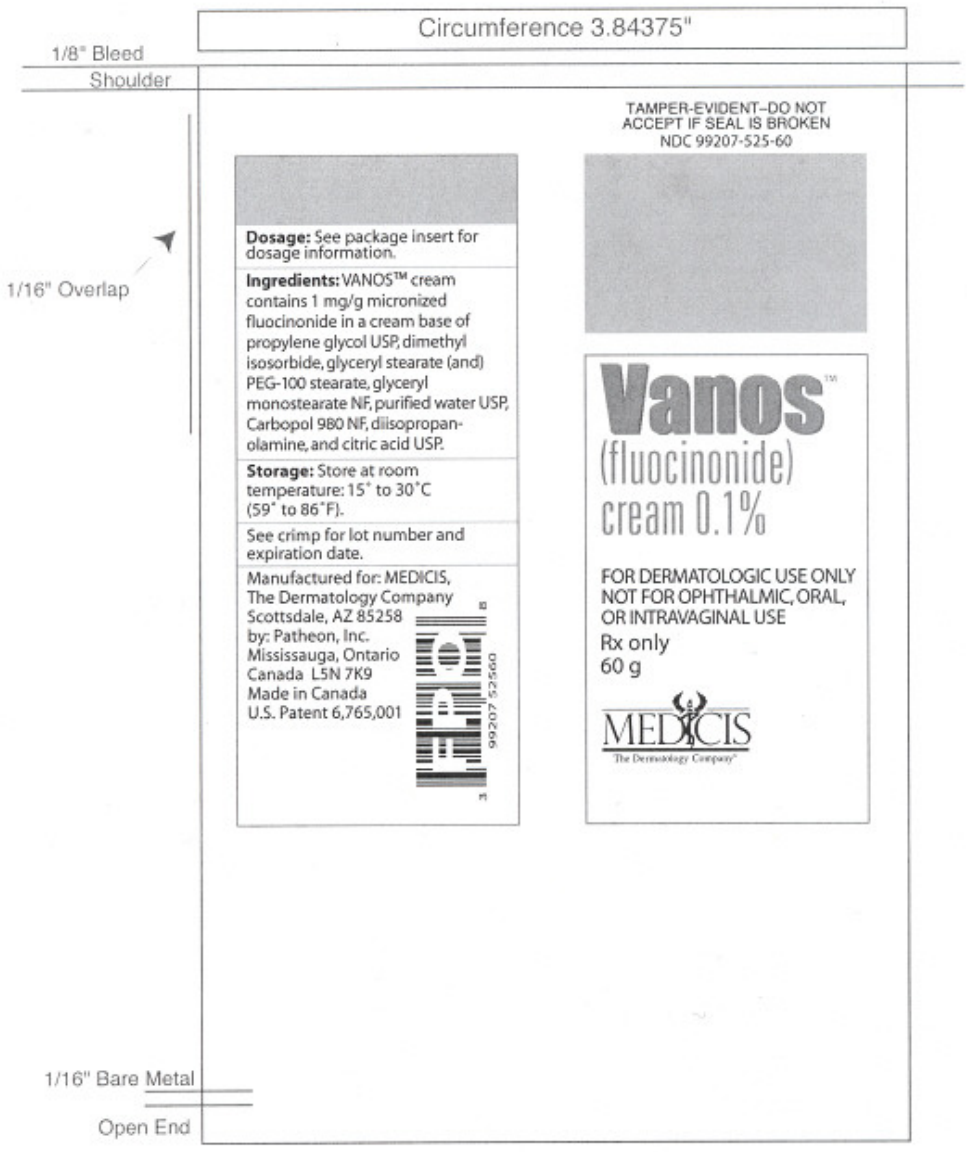
Storage: Store at room temperature: 15° to 30°C (59° to 86°F).

ULIDEX CREAM 0.1% 30g CARTON
8/30/04

PMS 151 | PMS 185 | PMS 293 | PMS 431

ULIDEX CREAM 0.01% 60g CARTON
8/30/04





ULIDEX CREAM 0.01% 60g TUBE
8/30/04