

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-300

APPROVED LABELING

(ENLARGED TO 115% by FOL STAFF)



fougera®

FLUTICASONE PROPIONATE OINTMENT, 0.005%

For Dermatologic Use Only

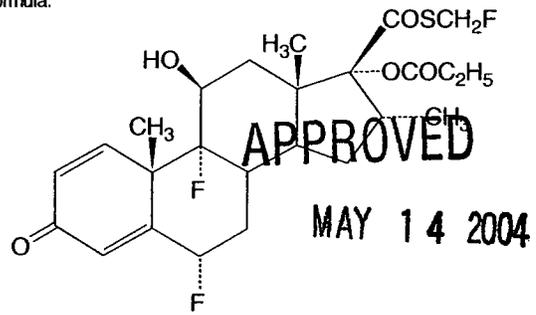
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Not for Ophthalmic Use

DESCRIPTION:

Fluticasone propionate ointment, 0.005% contains fluticasone propionate [(6 α , 11 β , 16 α , 17 α)-6,9,-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy) androsta-1,4-diene-17-carbothioic acid, S-fluoromethyl ester], a synthetic fluorinated corticosteroid, for topical dermatologic use. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents.

Chemically, fluticasone propionate is C₂₅H₃₁F₃O₅S. It has the following structural formula:



Fluticasone propionate has a molecular weight of 500.6. It is a white to off-white powder and is insoluble in water. Each gram of fluticasone propionate ointment contains fluticasone propionate 0.05 mg in a base of propylene glycol, sorbitan sesquioleate, microcrystalline wax, and liquid paraffin.

CLINICAL PHARMACOLOGY:

Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A₂ 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, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂.

Fluticasone propionate is lipophilic and has a strong affinity for the glucocorticoid receptor. It has weak affinity for the progesterone receptor, and virtually no affinity for the mineralocorticoid, estrogen, or androgen receptors. The therapeutic potency of glucocorticoids is related to the half-life of the glucocorticoid-receptor complex. The half-life of the fluticasone propionate-glucocorticoid receptor complex is approximately 10 hours.

Studies performed with fluticasone propionate ointment indicate that it is in the medium range of potency as compared with other topical corticosteroids.

Pharmacokinetics: Absorption: The activity of fluticasone propionate is due to the parent drug, fluticasone propionate. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.

In a study of 6 healthy volunteers applying 25 g of fluticasone propionate ointment 0.005% twice daily to the trunk and legs for up to 5 days under occlusion, plasma levels of fluticasone ranged from 0.08 to 0.22 ng/mL.

In an animal study using radiolabeled 0.05% fluticasone propionate cream and ointment preparations, rats received a topical dose of 1 g/kg for a 24-hour period. Total recovery of radioactivity was approximately 80% at the end of the 7 days. The majority of the dose (73%) was recovered from the surface of the application site. Less than 1% of the dose was recovered in the skin at the application site. Approximately 5% of the dose was absorbed systemically through the skin. Absorption from the skin continued for the duration of the study (7 days), indicating a long retention time at the application site.

Distribution: Following intravenous administration of 1 mg of fluticasone propionate in healthy volunteers, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid sol-

ubility and tissue binding. The apparent volume of distribution averaged 4.2 L/kg (range, 2.3-16.7 L/kg). The percentage of fluticasone propionate bound to human plasma proteins averaged 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism: No metabolites of fluticasone propionate were detected in an in vitro study of radiolabeled fluticasone propionate incubated in human skin homogenate. The total blood clearance of systemically absorbed fluticasone propionate averages 1093 mL/min (range, 618-1702 mL/min) after a 1-mg intravenous dose, with renal clearance accounting for less than 0.02% of the total. Fluticasone propionate is metabolized in the liver by cytochrome P450 3A4-mediated hydrolysis of the 5-fluoromethyl carbothioate grouping. This transformation occurs in 1 metabolic step to produce the inactive 17- β -carboxylic acid metabolite, the only known metabolite detected in man. This metabolite has approximately 2000 times less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Excretion: Following an intravenous dose of 1 mg in healthy volunteers, fluticasone propionate showed polyexponential kinetics and had an average terminal half-life of 7.2 hours (range, 3.2-11.2 hours).

INDICATIONS AND USAGE:

Fluticasone propionate ointment is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS:

Fluticasone propionate ointment 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 from 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.

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 the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol 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 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.

A concentrated fluticasone propionate ointment, 0.05% (10 times that of the marketed fluticasone propionate ointment, 0.005%) suppressed 24-hour urinary free cortisol levels in 2 of 6 patients when used at a dose of 30 g/day for a week in patients with psoriasis or atopic eczema. No suppression of A.M. plasma cortisol was observed. In a second study of the same concentrated formulation of fluticasone propionate ointment, 0.05%, depression of A.M. plasma cortisol levels was noted in 2 of 8 normal volunteers when applied at doses of 50 g/day for 21 days. Morning plasma levels returned to normal levels within 4 days upon discontinuation of fluticasone propionate. In this study there was no corresponding decrease in 24-hour urinary free cortisol levels.

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**.)

Fluticasone propionate ointment, 0.005% may cause local cutaneous adverse reactions (see **ADVERSE REACTIONS**).

If irritation develops, fluticasone propionate ointment should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a

(over)

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 fluticasone propionate ointment should be discontinued until the infection has been adequately controlled.

Fluticasone propionate ointment should not be used in the presence of pre-existing skin atrophy and should not be used where infection is present at the treatment site. Fluticasone propionate ointment should not be used in the treatment of rosacea and perioral dermatitis.

Information for Patients:

Patients using topical corticosteroids 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. This medication 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. This medication should not be used on the face, underarms, or groin areas unless directed by a physician.
6. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

Laboratory Tests: The following tests may be helpful in evaluating patients for HPA axis suppression:

- ACTH stimulation test
- A.M. plasma cortisol test
- Urinary free cortisol test

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Two 18-month studies were performed in mice to evaluate the carcinogenic potential of fluticasone propionate when given topically (as an 0.05% ointment) and orally. No evidence of carcinogenicity was found in either study.

Fluticasone propionate was not mutagenic in the standard Ames test, *E. coli* fluctuation test, *S. cerevisiae* gene conversion test or Chinese Hamster ovarian cell assay. It was not clastogenic in mouse micronucleus or cultured human lymphocyte tests.

In a fertility and general reproductive performance study in rats, fluticasone propionate administered subcutaneously to females at up to 50 mcg/kg per day and to males at up to 100 mcg/kg per day (later reduced to 50 mcg/kg per day) had no effect upon mating performance or fertility. These doses are approximately 150 and 300 times, respectively, the human systemic exposure following use of the recommended human topical dose of fluticasone propionate ointment, 0.005%, assuming human percutaneous absorption of approximately 3% and the use in a 70-kg person of 15 g/day.

Pregnancy: Teratogenic Effects: Pregnancy Category C. 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. Teratology studies in the mouse demonstrated fluticasone propionate to be teratogenic (deft palate) when administered subcutaneously in doses of 45 mcg/kg per day and 150 mcg/kg per day. This dose is approximately 140 and 450 times, respectively, the human topical dose of fluticasone propionate ointment, 0.005%. There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate ointment 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 human milk. Because many drugs are excreted in human milk, caution should be exercised when fluticasone propionate ointment is administered to a nursing woman.

Pediatric Use: 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 pediatric patients.

HPA axis suppression, Cushing's Syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Geriatric Use: A limited number of patients above 65 years of age (n=203) have been treated with fluticasone propionate ointment in US and non-US clinical trials. While the number of patients is too small to permit separate analysis of efficacy and safety, the adverse reactions reported in this population were similar to those reported by younger patients. Based on available data, no adjustment of dosage of fluticasone in geriatric patients is warranted.

ADVERSE REACTIONS:

In controlled clinical trials, the total incidence of adverse reactions associated with the use of fluticasone propionate ointment was approximately 4%. These adverse reactions were usually mild, self-limiting, and consisted primarily of pruritus, burning, hypertrichosis, increased erythema, hives, irritation, and fightheadedness. Each of these events occurred individually in less than 1% of patients.

The following additional local adverse reactions have been reported infrequently with topical corticosteroids, including fluticasone propionate, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria. Also, there are reports of the development of pustular psoriasis from chronic plaque psoriasis following reduction or discontinuation of potent topical corticosteroid products.

OVERDOSAGE:

Topically applied fluticasone propionate ointment can be absorbed in sufficient amounts to produce systemic effects (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION:

Apply a thin film of fluticasone propionate ointment to the affected skin areas twice daily. Rub in gently.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see **PRECAUTIONS**) have been treated with fluticasone propionate ointment, safety did not differ from that in younger patients; therefore, no dosage adjustment is recommended.

HOW SUPPLIED:

Fluticasone Propionate Ointment, 0.005% is supplied in:

- 15 g tubes NDC 0168-0333-15
- 30 g tubes NDC 0168-0333-30
- 60 g tubes NDC 0168-0333-60

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

E. FOUGERA & CO.

a division of Altana Inc.
MELVILLE, NEW YORK 11747

12333
R7/02
#79



2.281

NDC 0168-0333-15

fougera[®]

**FLUTICASONE
PROPIONATE OINTMENT,
0.005%**

APPROVED

MAY 14 2004

NET WT 15 grams

R only

FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC USE

Each gram contains: Fluticasone propionate 0.005% in an ointment base of propylene glycol, sorbitan sesquioleate, microcrystalline wax, and liquid paraffin.

Usual Dosage: Apply a thin film of ointment to the affected skin areas twice daily.
See package insert for full prescribing information.
Store between 2° and 30°C (36° and 86°F).

TO OPEN: Use cap to puncture seal.

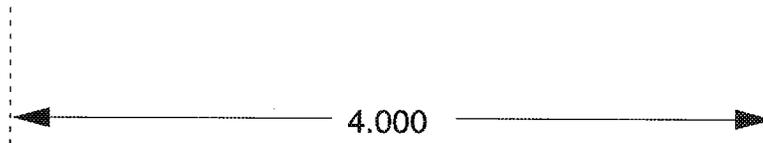
IMPORTANT: Do not use if seal has been punctured or is not visible.

WARNING: Keep out of reach of children.
See top of tube for Lot Number and Expiration Date.

R7/02 U4974

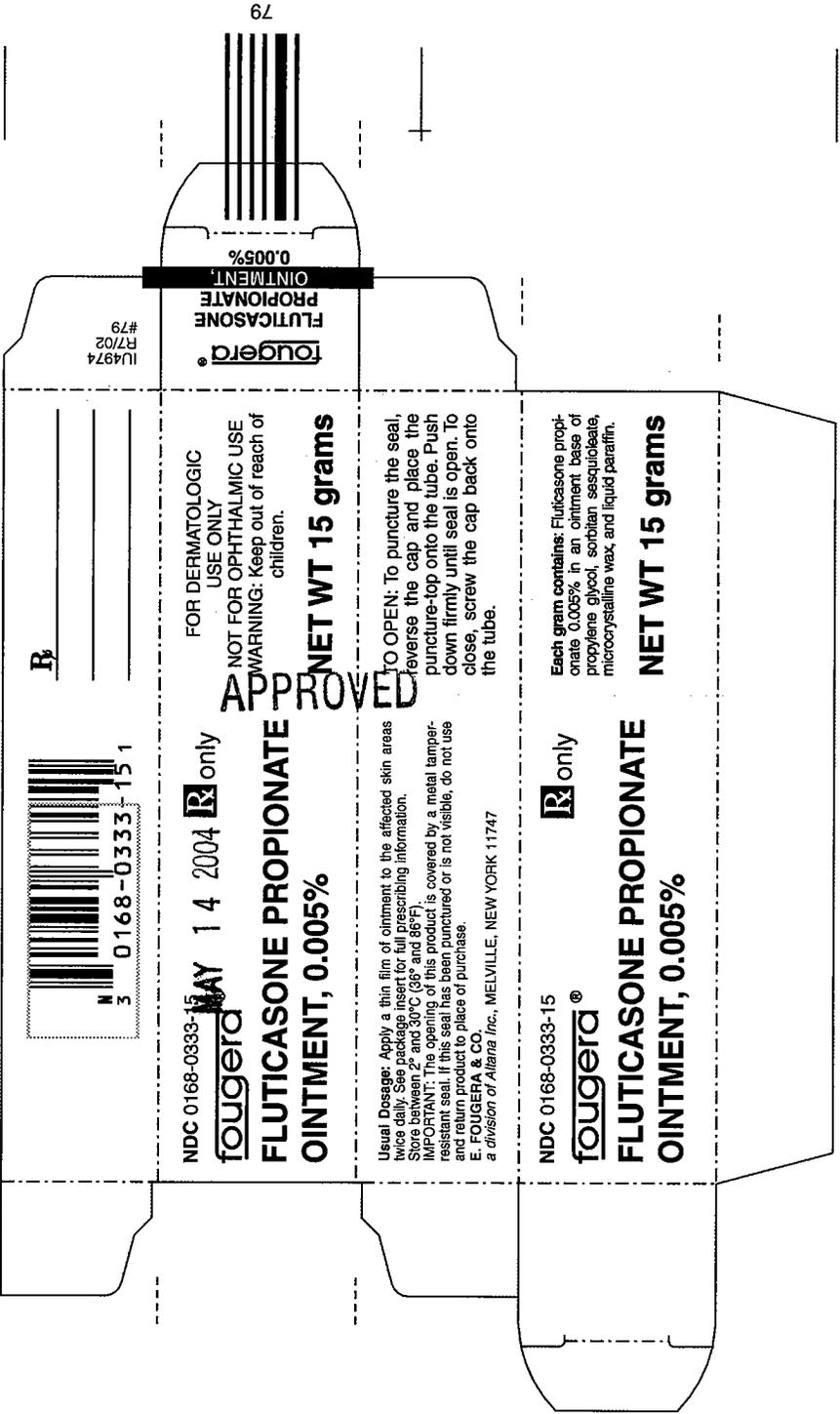
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a division of Altana Inc.
MELVILLE, NEW YORK 11747

0168-0333-15 1



Name: FLUTICASONE PROPIONATE 0.005% Ointment 15 g
SST-55 *** Bare metal is .1250" spec may need to be revised
Die Size: 4 x 2.281 CIRC:
UPC Code: 0168-0333-15
Pharma Code: # 79 Colors: PMS Yellow PMS Black

Draft labeling prepared from innovator sample
Cutivate/ spell checked AA-11/12/01
FDA Letter AA-7/9/02



NDC 0168-0333-15
fougera
 MAY 14 2004 **R** only
FLUTICASONE PROPIONATE OINTMENT, 0.005%
NET WT 15 grams

fougera
 FLUTICASONE PROPIONATE OINTMENT
 0.005%

APPROVED
 FOR DERMATOLOGIC USE ONLY
 NOT FOR OPHTHALMIC USE
 WARNING: Keep out of reach of children.

Usual Dosage: Apply a thin film of ointment to the affected skin areas twice daily. See package insert for full prescribing information. Store between 2° and 30°C (36° and 86°F).
 IMPORTANT: The opening of this product is covered by a metal tamper-resistant seal. If this seal has been punctured or is not visible, do not use and return product to place of purchase.
 E. FOUGERA & CO.
 a division of Alliana Inc., MELVILLE, NEW YORK 11747

R only
FLUTICASONE PROPIONATE OINTMENT, 0.005%
NET WT 15 grams

R only
FLUTICASONE PROPIONATE OINTMENT, 0.005%
NET WT 15 grams

Name: FLUTICASONE PROPIONATE 0.005% OINTMENT
 SSC-4
 Die Size: 1.062 x .875 x 4.250
 UPC Code: 0168-0333-15 Pharma Code: #79
 Colors: PMS Yellow PMS Black

Draft labeling prepared from innovator sample
 Cutivate/ spell checked
 FDA letter
 AA-11/12/01
 AA-7/9/02

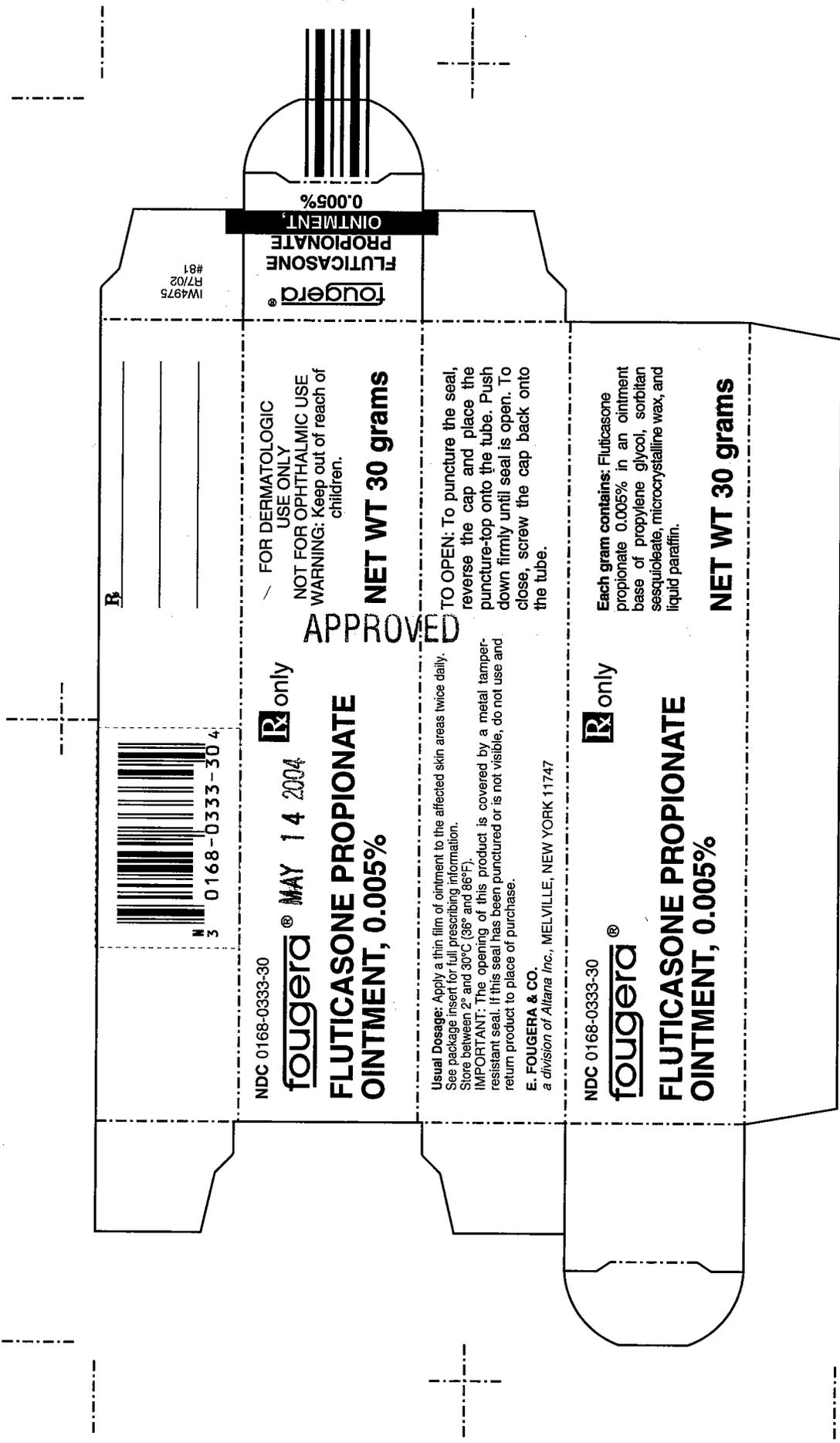
T7420

30 GRZ CTN

1.218 x 1 x 5.4375(ext 1/8th inch)

WARNING!
DO NOT MODIFY DIE LINL

PRINT SIDE SHOWING



18

60

Name: FLUTICASON PROPIONATE 0.005% 30 g
 SSC-7
 Die Size: 1.218 x 1.000 x 5.4375
 UPC Code: 0168-0333-30 Pharma Code: #81
 Colors: PMS Yellow PMS Black

Draft labeling prepared from innovator
 sample Cutivate/ spell checked
 FDA Letter
 AA-11/12/01
 AA-7/9/02

3.468

NDC 0168-0333-60

fougera[®]

**FLUTICASONE
PROPIONATE OINTMENT,
0.005%**

MAY 14 2004

Usual Dosage: Apply a thin film of ointment to the affected skin areas twice daily.
See package insert for full prescribing information.
Store between 2° and 30°C (36° and 86°F).

TO OPEN: Use cap to puncture seal.
IMPORTANT: Do not use if seal has been punctured or is not visible.

E. FOUGERA & CO.
a division of Altana Inc.
MELVILLE, NEW YORK 11747

R only

FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC USE
Each gram contains: Fluticasone propionate 0.005% in an ointment base of propylene glycol, sorbitan sesquioleate, microcrystalline wax, and liquid paraffin.

NET WT 60 grams

APPROVED

WARNING: Keep out of reach of children.

See crimp of tube for Lot Number and Expiration Date.

R7/02

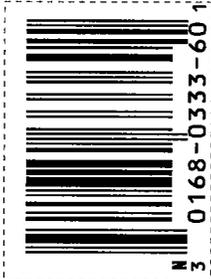
X4976



6.000

Name: Fluticasone Ointment 0.005%% 60 g
SST-19
DIMENSIONS 6.00" x 1.1250" CIRC: 3.4687
UPC: 0168-0278-60
PHARMACODE #83 COLORS:Process Yellow, black

Draft labeling prepared from innovator sample
Cutivate/ spell checked AA-11/12/01
FDA Letter AA-7/9/02



NDC 0168-0333-60

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MAY 14 2004 **R** only

FLUTICASONE PROPIONATE OINTMENT, 0.005%

APPROVED

FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC USE
WARNING: Keep out of reach of children.

NET WT 60 grams

Usual Dosage: Apply a thin film of ointment to the affected skin areas twice daily. See package insert for full prescribing information.
Store between 2° and 30°C (36° and 86°F).
IMPORTANT: The opening of this product is covered by a metal tamper-resistant seal. If this seal has been punctured or is not visible, do not use and return product to place of purchase.

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NDC 0168-0333-60

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R only

FLUTICASONE PROPIONATE OINTMENT, 0.005%

Each gram contains: Fluticasone propionate 0.005% in an ointment base of propylene glycol, sorbitan sesquioleate, microcrystalline wax, and liquid paraffin.

NET WT 60 grams

Name: FLUTICASONE PROPIONATE 0.005% 60g Cart
SSC-10

Die Size: 1.375" x 1.375" x 6.1875"

UPC Code: 0168-0333-60 Pharma Code: #83

Colors: Process Yellow PMS Black

Draft labeling prepared from innovator sample
Cutivate/ spell checked
FDA Letter

AA-11/12/01
AA-7/9/02

IX4976
R7/02
#83

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FLUTICASONE PROPIONATE OINTMENT, 0.005%