CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-374

APPROVED DRAFT LABELING

fougera®

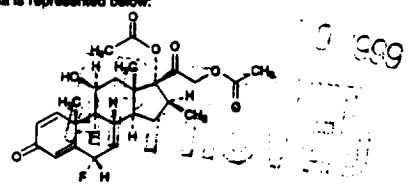
DIFLORASONE DIACETATE OINTMENT USP, 0.05%

℞ only

FOR EXTERNAL USE ONLY NOT FOR OPHTHALMIC USE

DESCRIPTION: Diflorasone diacetate ointment contains 0.5 mg diflorasone diacetate in an ointment base.

Chemically, diflorasone diacetate is 6α,9-difluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21- diacetate with the molecular formula $C_{26}H_{32}F_2O_7$ and a molecular weight of 494.54. The structural formula is represented below:



Each gram of diflorasone diacetate ointment, for topical administration, contains 0.5 mg diflorasone diacetate in an ointment base consisting of propylene glycol, glyceryl monostearate and white petrolatum.

CLINICAL PHARMACOLOGY: Topical corticosteroids share anti-inflammatory, anti-pruritic and vasoconstrictive actions.

The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

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.

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. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses. (See DOSAGE AND ADMINISTRATION.)

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. They 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.

INDICATIONS AND USAGE: Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS: Topical steroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS: General: Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, 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.

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing 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.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See PRECAUTIONS: Pediatric Use.)

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial

(over)

agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

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. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions especially under occlusive dressing.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

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

Urinary free cortisol test
ACTH-stimulation test

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

Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy: Teratogenic effects – *Pregnancy Category C.* 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 topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use: *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 pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients 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 corticosteroids to pediatric patients 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.

ADVERSE REACTIONS: The following local adverse reactions have been reported with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence:

1. Burning
2. Itching
3. Irritation
4. Dryness
5. Folliculitis
6. Hypertrichosis
7. Acneiform eruptions
8. Hypopigmentation
9. Perioral dermatitis
10. Allergic contact dermatitis
11. Maceration of the skin
12. Secondary infections
13. Skin atrophy
14. Striae
15. Miliaria

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

DOSAGE AND ADMINISTRATION: Diflorasone diacetate ointment should be applied to the affected area as a thin film from one to three times daily depending on the severity or resistant nature of the condition.

Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions.

If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy initiated.

HOW SUPPLIED: Diflorasone Diacetate Ointment USP, 0.05% is available in the following size tubes:

NDC 0168-0243-15	15 gram tube
NDC 0168-0243-30	30 gram tube
NDC 0168-0243-60	60 gram tube

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

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

I243
#188
R10/98

NDC 0168-0243-60

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℞ only

DIFLORASONE DIACETATE OINTMENT USP, 0.05%

FOR EXTERNAL USE ONLY
NOT FOR OPHTHALMIC USE

WARNING: Keep out of reach of children.

NET WT 60 grams

USUAL DOSAGE: Apply to affected area 1 to 3 times daily.
See package insert for full prescribing information.
Store at controlled room temperature 15°-30°C (59°-86°F). Keep tightly closed.
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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TO OPEN: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open.

To close, screw the cap back onto the tube.

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DIFLORASONE DIACETATE OINTMENT USP, 0.05%

PRINT SIDE
1-3/8 X 1-3/8 X 6-3/16

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Pharma :#233
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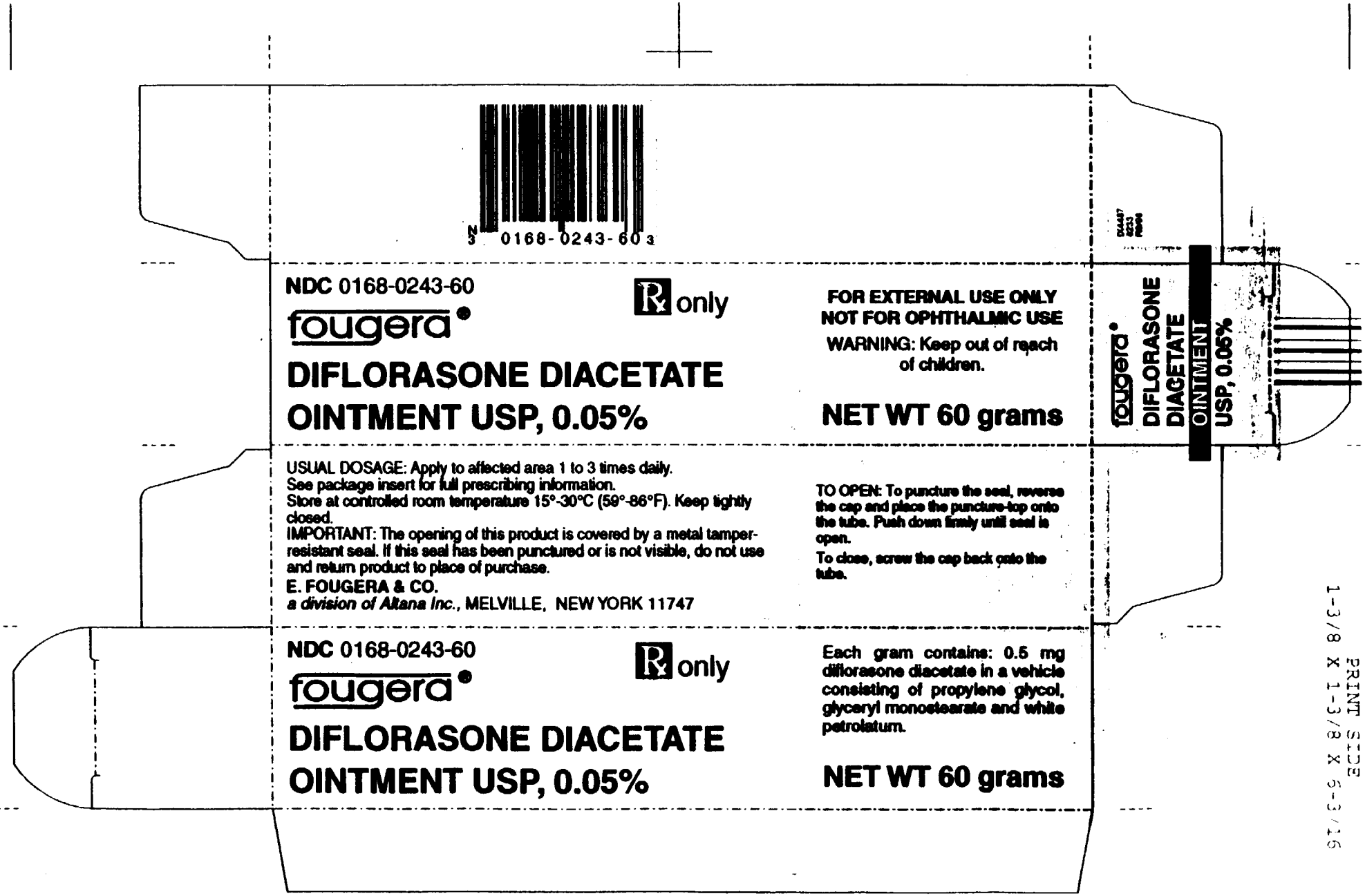
Colors :Black, Process Yellow



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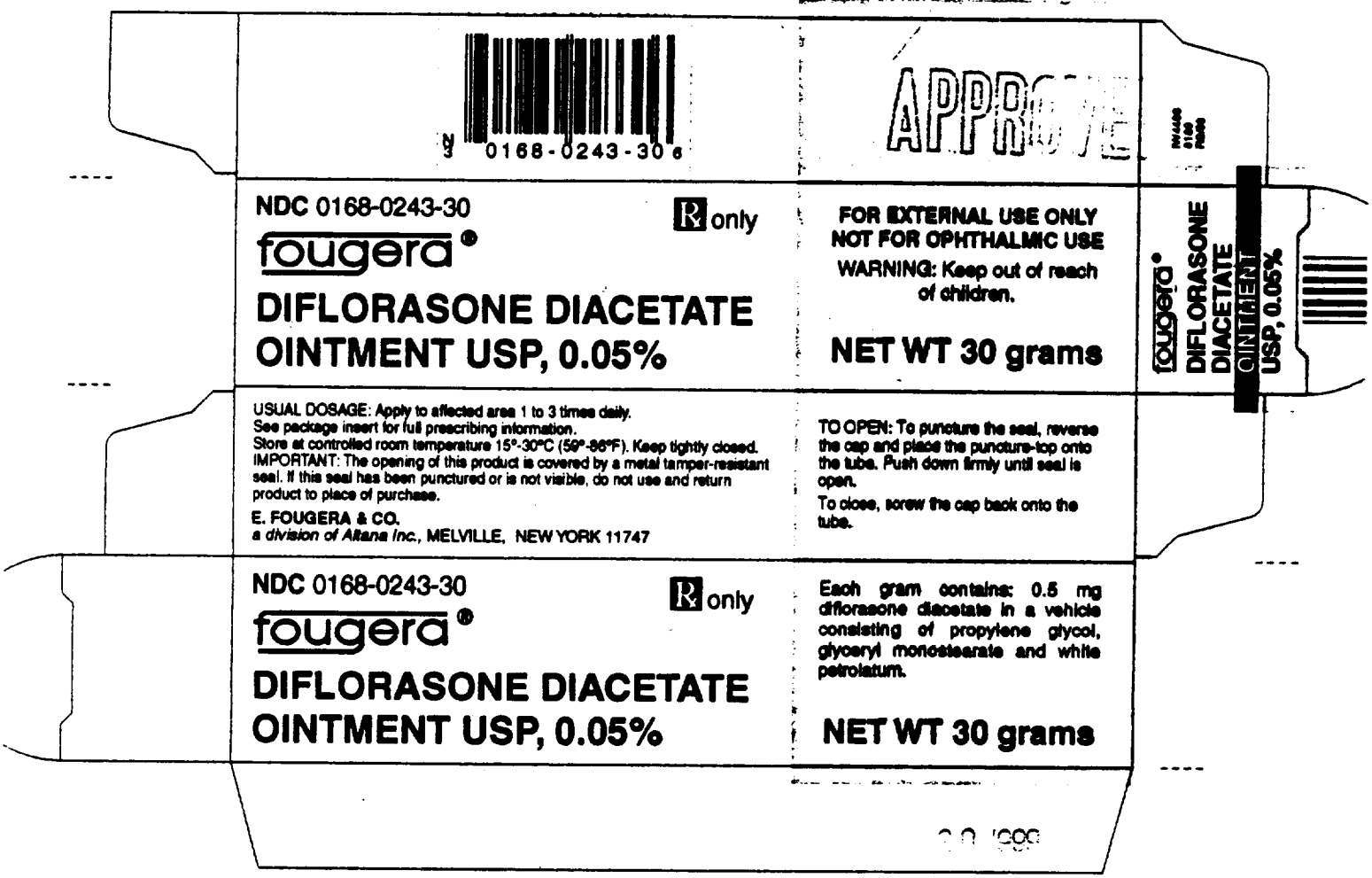

NDC 0168-0243-30

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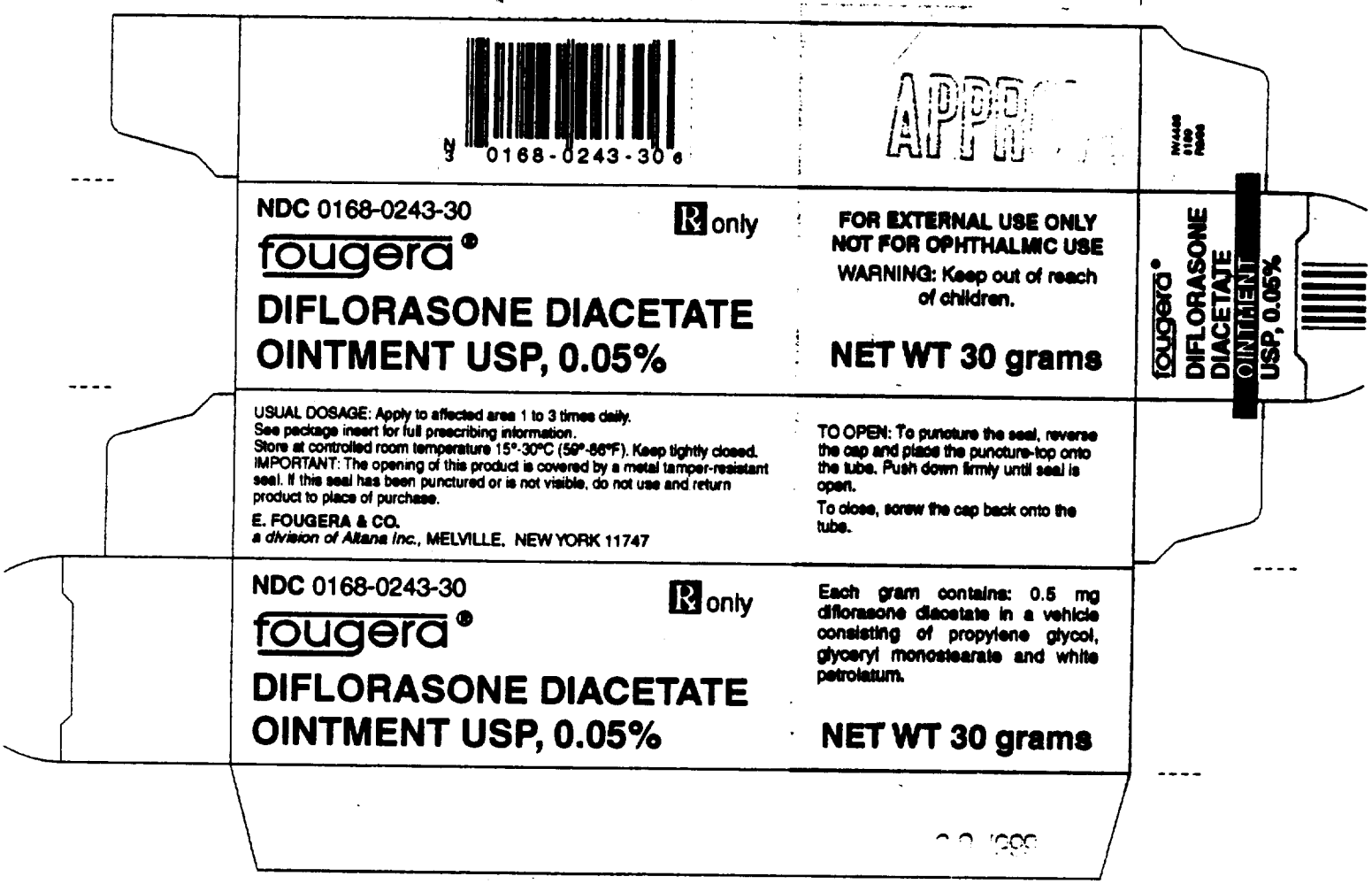

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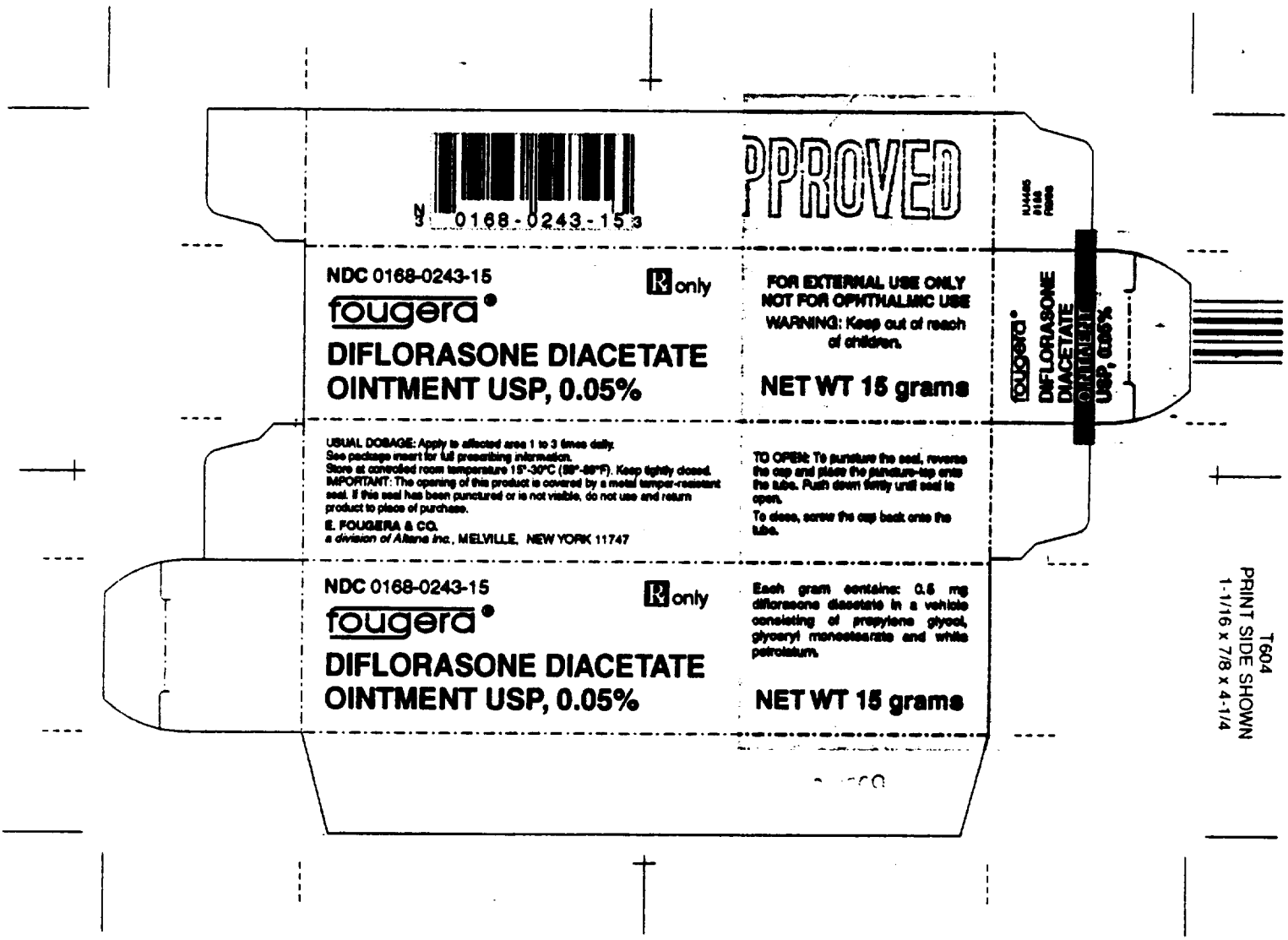

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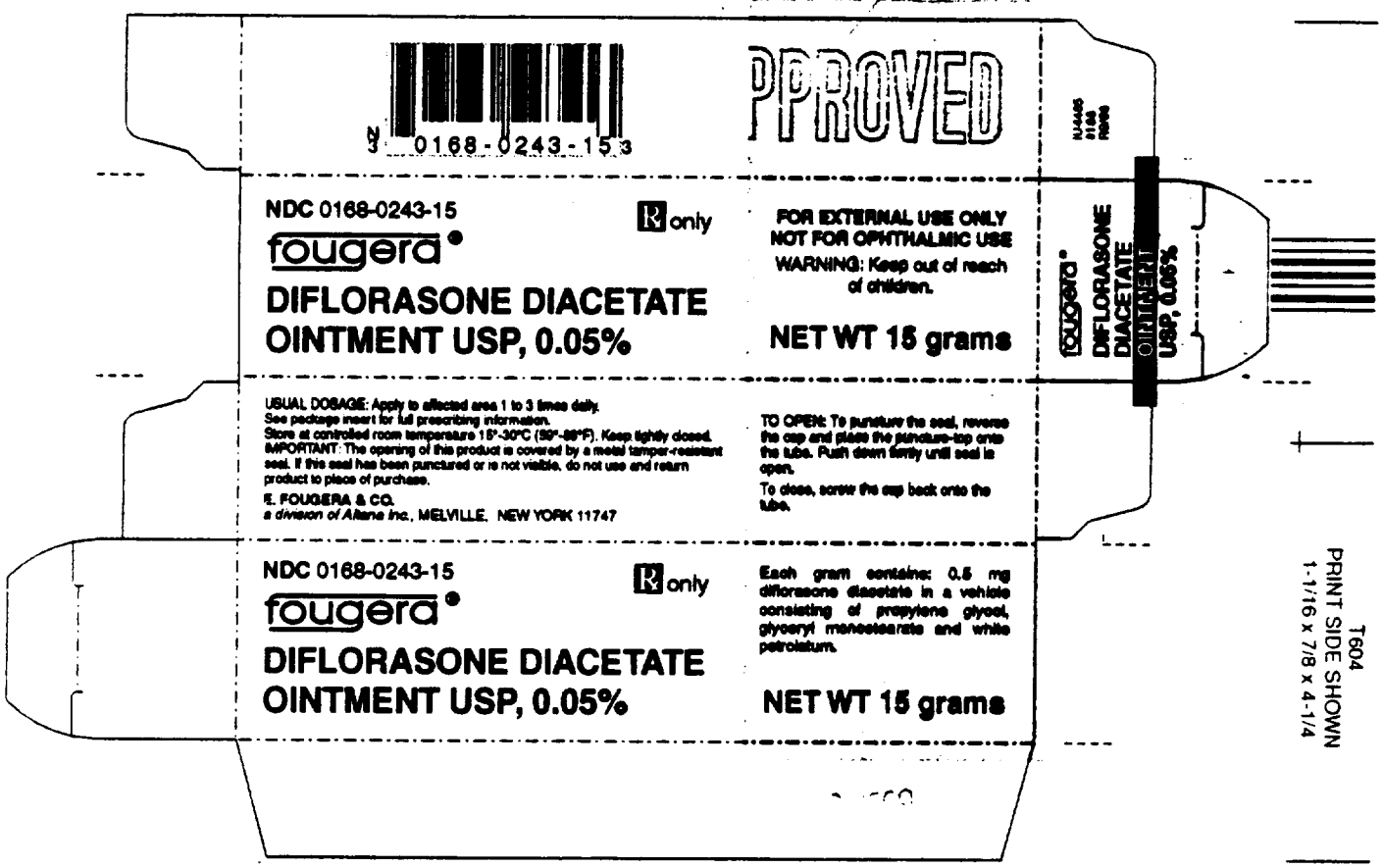
Colors: Black, Process Yellow



Item# :IU4485
Die Size:1.063" x .875" x 4.250"
Pharma: #166
Colors: Black, Process Yellow

NDC 0168-0243-60

fougera®

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

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Each gram contains: 0.5 mg diflorasone diacetate in a vehicle consisting of propylene glycol, glyceryl monostearate and white petrolatum.

NET WT 60 grams

Store at controlled room temperature 15°-30°C (59°-86°F).
Keep tightly closed.
See crimp of tube for Lot No. and Exp. Date

X4487 R9/98

N 3 0168-0243-60 3

3.468

Item# :X4487
Die Size: 1.125" x 6.00"
Pharma :#233
Colors: Black, Process Yellow

6.000

3.468

NDC 0168-0243-60

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N 3 0168-0243-60 3

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Pharma :#233
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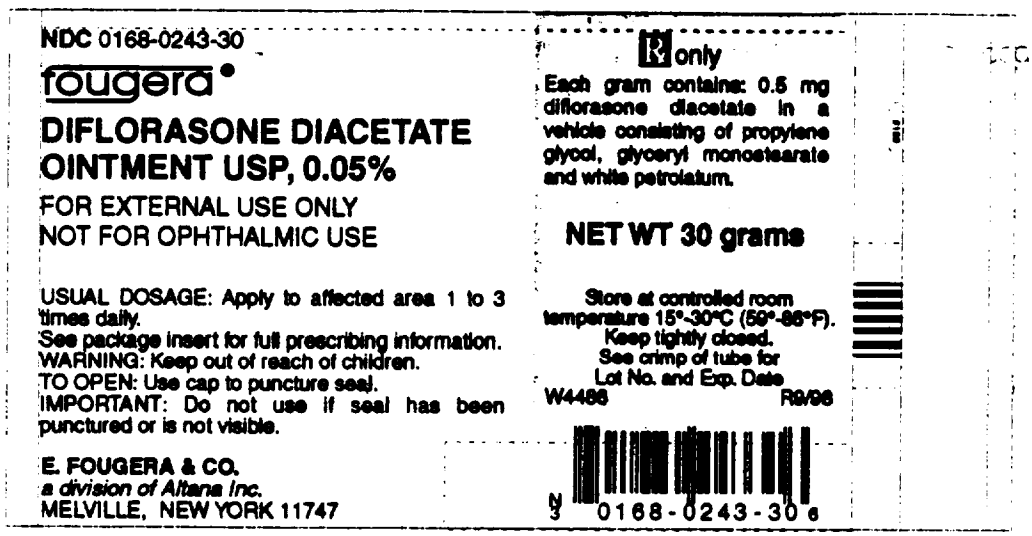
6.000



2.687

Item# W4486
Die Size:.875" x 5.25"
Pharma #189
Colors Black, Process Yellow

5.250

2.687

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W4486 R9/96

N 3 0168-0243-30 6

Item# W4486
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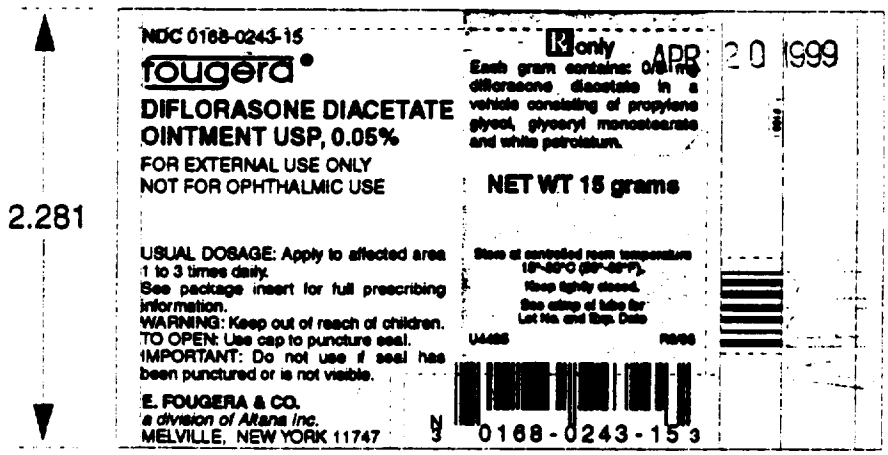
Pharma #189
Colors Black, Process Yellow

5.250



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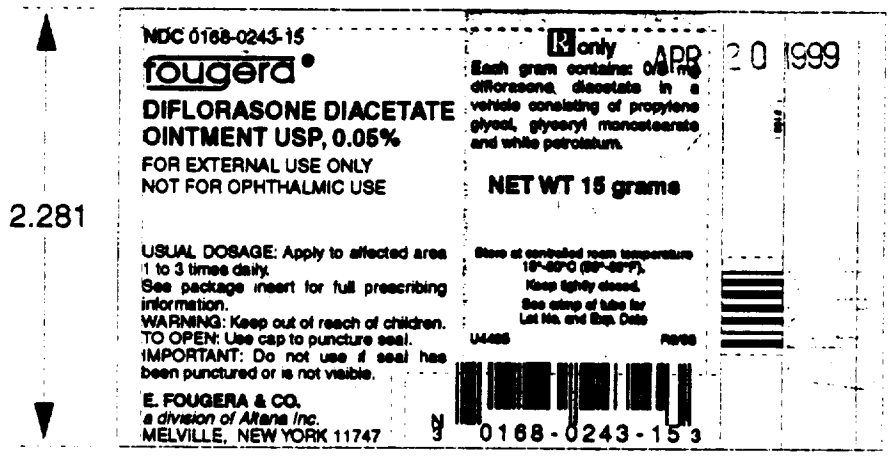
Pharma #188
Colors Black, Process Yellow

4.000



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4.000