CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 75187

Trade Name Diflorasone Diacetate Cream USP 0.05%

Generic Name Diflorasone Diacetate Cream USP 0.05%

Sponsor Altana, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 75187

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75187

APPROVAL LETTER

ANDA 75-187

MAR 30 1998

Altana Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

Dear Madam:

This is in reference to your abbreviated new drug application dated August 20, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Diflorasone Diacetate Cream USP, 0.05%.

Reference is also made to your amendments dated January 22, February 4, March 6, and March 10, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Diflorasone Diacetate Cream USP, 0.05% to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Psorcon Cream, 0.05% of Dermik Laboratories, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

3/30/98

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75187

FINAL PRINTED LABELING

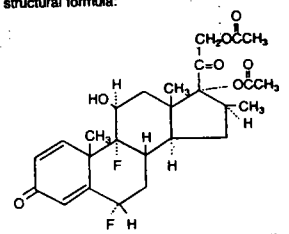
fougera® MAR 30 1998

DIFLORASONE DIACETATE CREAM USP, 0.05%

FOR EXTERNAL USE ONLY **NOT FOR OPHTHALMIC USE**

DESCRIPTION: Diflorasone diacetate cream, 0.05% contains the active compound diflorasone diacetate, a synthetic corticosteroid for topical dermatological use.

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 $C_{26}H_{32}F_2O_7$, a molecular weight of 494.54, and the following structural formula:



Each gram of diflorasone diacetate cream, 0.05% contains: 0.5 mg diflorasone diacetate in a cream base consisting of cetyl alcohol, glyceryl stearate SE (nonionic), isopropyl myristate, mineral oil (and) lanolin alcohol, monobasic sodium phosphate, monoglyceride citrate, polyoxyl 40 stearate, polysorbate 60, propylene glycol, purified water, sorbitan monostearate, vegetable oil, butylated hydroxytoluene and citric acid.

CLINICAL PHARMACOLOGY: Like other topical corticosteroids, diflorasone diacetate has anti-inflammatory, anti-pruritic, and vasoconstrictive actions. The mechanism of the anti-inflammatory activity of the topical corticosteroids, in general, is unclear. However, corticosteroids are thought to act by the 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, arachidonic acid. Arachidonic 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. Studies performed with diflorasone diacetate cream indicate that it is in the high range of potency as compared with other topical corticosteroids.

INDICATIONS AND USAGE: Diflorasone diacetate cream USP, 0.05% is a high potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS: Diflorasone diacetate 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.

Patients receiving a large dose of a higher potency topical steroid applied to a large surface area or under an occlusive dressing 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.

This product has a greater ability to produce adrenal suppression than does diflorasone diacetate ointment, 0.05%. At 30 g per day (applied as 15 g twice daily) diflorasone diacetate cream, 0.05% was shown to cause inhibition of the HPA axis in one of two patients following application for one week to psoriatic skin. At 15 g per day (applied as 7.5 g twice daily) diflorasone diacetate cream was shown to cause mild inhibition of the HPA axis in one of five patients following application for one week to diseased skin (psoriasis or atopic dermatitis). These effects were reversible upon discontinuation of treatment. By comparison, diflorasone diacetate ointment 0.05% did not produce significant HPA axis suppression when used in divided doses at 30 g per day for one week in patients with psoriasis or atopic dermatitis.

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 and complete 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.

(over)

Children 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, diflorasone diacetate 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 diflorasone diacetate cream should be discontinued until the infection has been adequately controlled.

Diflorasone diacetate cream should not be used in the treatment of rosacea or perioral dermatitis, and it should not be used on the face, groin, or axillae.

Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:

1) The medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2) The 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.

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, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of diflorasone diacetate.

Diflorasone diacetate was not found to be mutagenic in a micronucleus test in rats at dosages of 2400 mg/kg.

Studies in the rat following topical administration at doses up to 0.5 mg/kg revealed no effects on fertility.

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 to laboratory animals.

Diflorasone diacetate has been shown to be teratogenic (cleft palate) in rats when applied topically at a dose of approximately 0.001 mg/kg/day to the shaven thorax of pregnant animals. This is approximately 0.3 times the human topical dose of diflorasone diacetate cream. When pregnant rats were treated topically with approximately 0.5 mg/kg/day, uterine deaths were higher in the treated animals than in control animals.

In rabbits, cleft palate was seen when diflorasone diacetate was applied in topical doses as low as 20 mg/kg/day. In addition, fetal weight was depressed and litter sizes were smaller.

There are no adequate and well-controlled studies of the teratogenic potential of diflorasone diacetate in pregnant women. Diflorasone diacetate 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 human milk. Because many drugs are excreted in human milk, caution should be exercised when diflorasone diacetate cream is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of diflorasone diacetate cream 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 when they are treated with topical corticosteroids. They are, therefore, also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and pediatric patients.

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.

ADVERSE REACTIONS: The following local adverse reactions have been reported infrequently with other topical corticosteroids, and they may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infections, skin atrophy, striae, and miliaria.

OVERDOSAGE: Topically applied diflorasone diacetate cream, can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION: Diflorasone Diacetate Cream USP, 0.05% should be applied to the affected area twice daily.

HOW SUPPLIED: Diflorasone Diacetate Cream USP, 0.05% is available as follows:

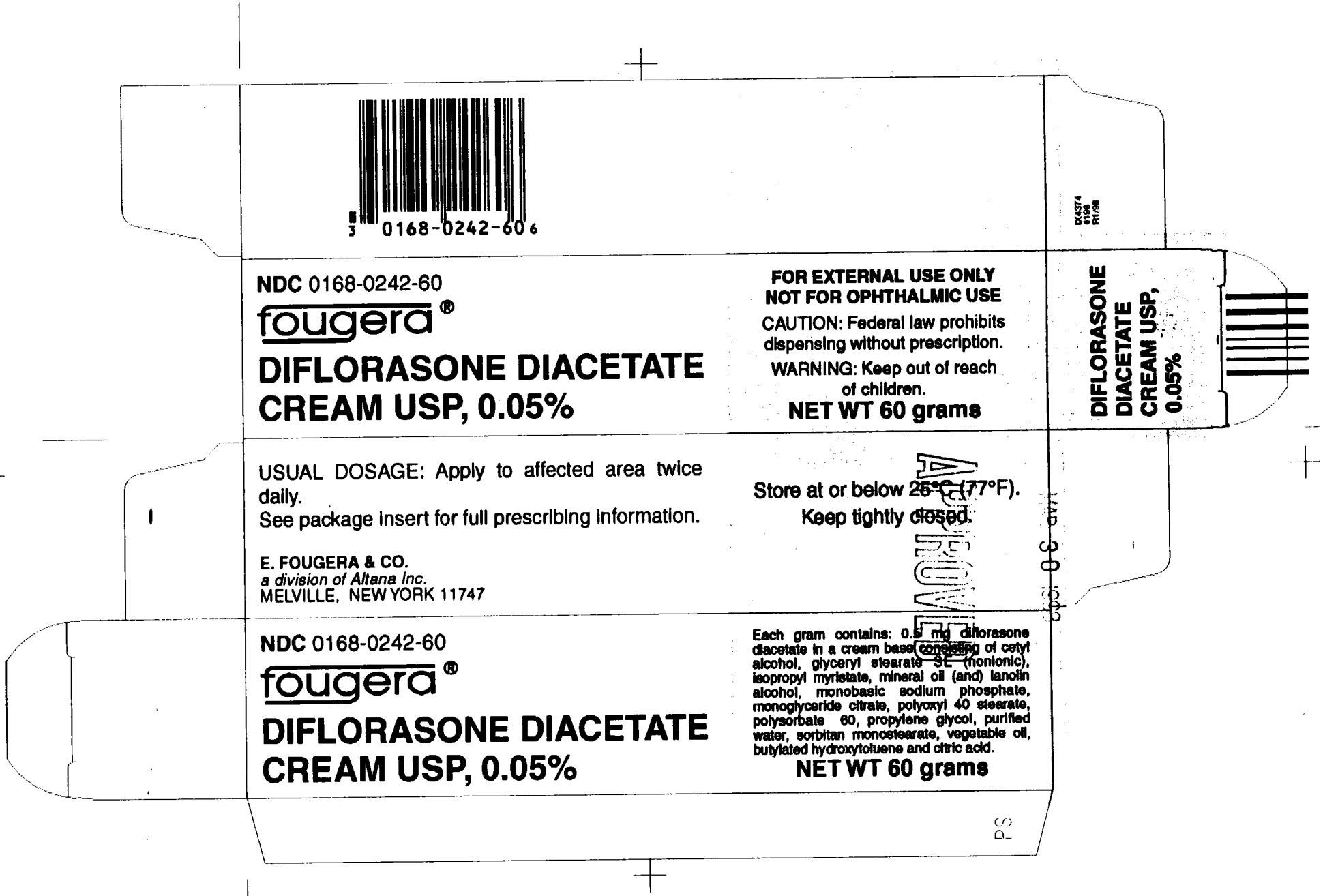
NDC 0168-0242-15	15 gram tube
NDC 0168-0242-30	30 gram tube
NDC 0168-0242-60	60 gram tube

Store at or below 25°C (77°F). Keep tightly closed.

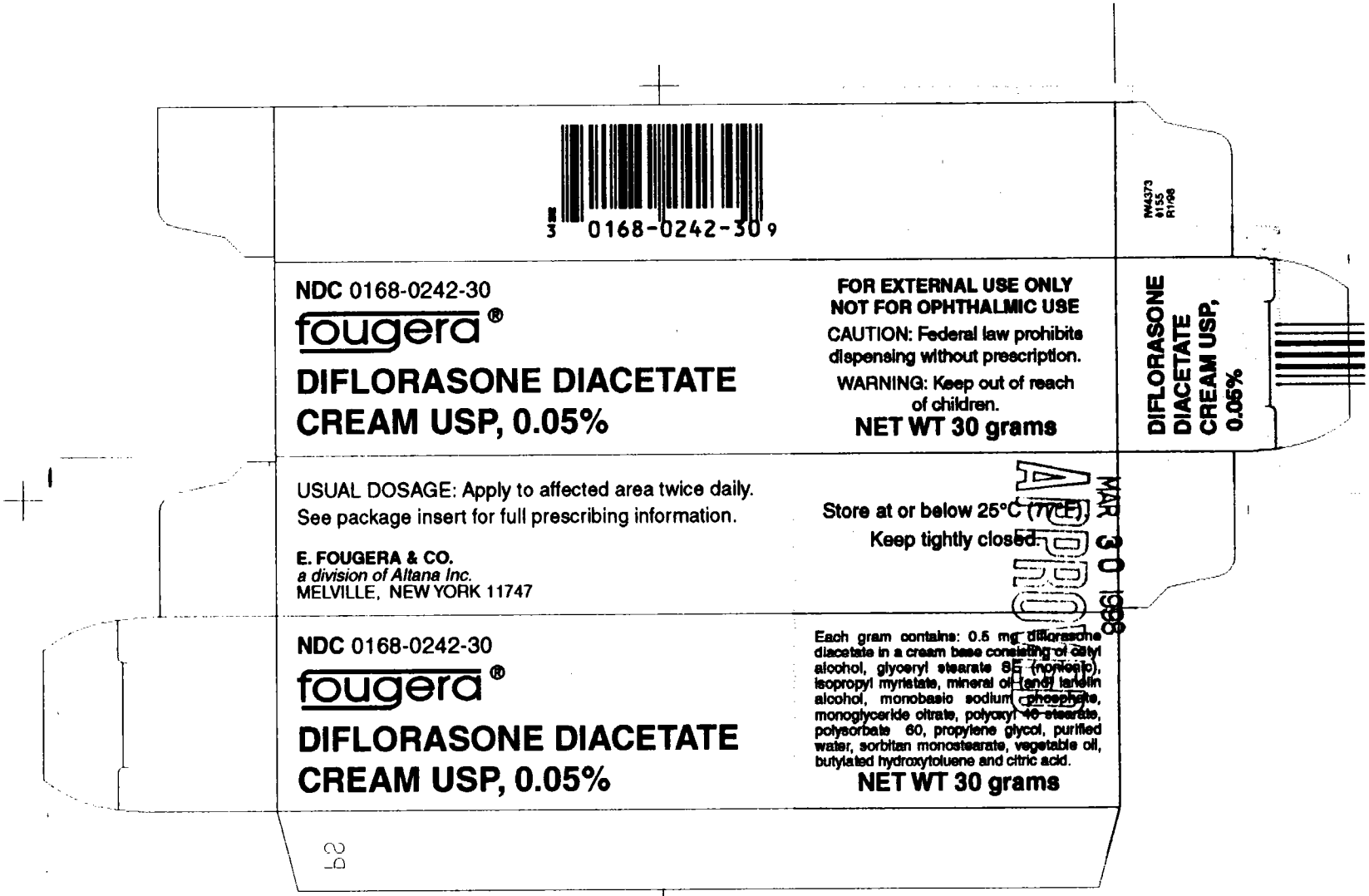
Caution: Federal law prohibits dispensing without prescription.

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

I242
#171
R2/98



Item# IX4374
Die Size:
Pharma #198
Colors Black, Process Yellow



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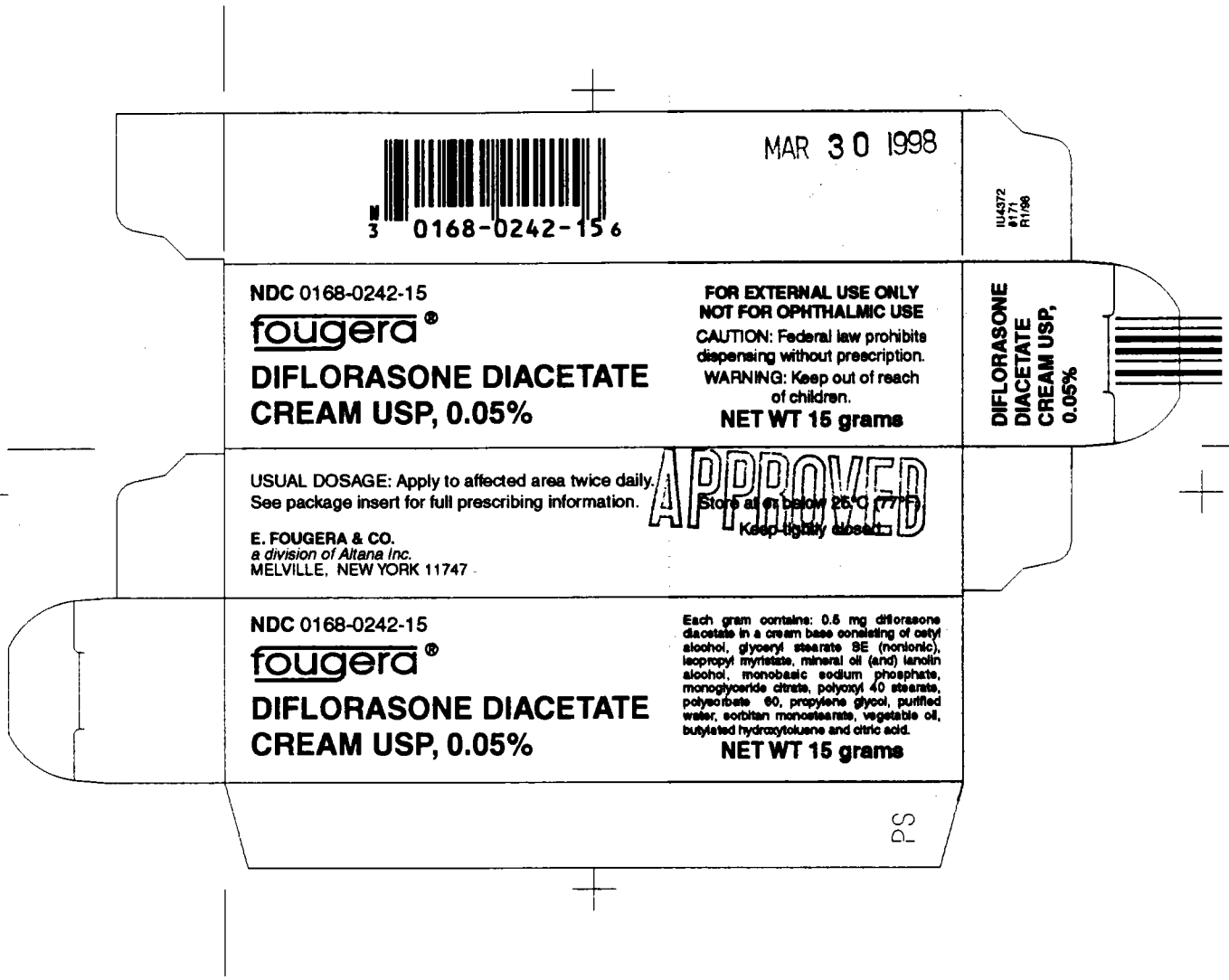
Pharma #155
Colors Black, Process Yellow

1.063 x .875 x 4.25



Item# IU4372
Die Size:
Pharma # 171
Colors Black, Process Yellow

NDC 0168-0242-60

fougera®

DIFLORASONE DIACETATE CREAM USP, 0.05%

FOR EXTERNAL USE ONLY
NOT FOR OPHTHALMIC USE

USUAL DOSAGE: Apply to affected area twice daily.
See package insert for full prescribing information.
CAUTION: Federal law prohibits dispensing without prescription.
WARNING: Keep out of reach of children.

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

Each gram contains: 0.5 mg diflorasone diacetate in a cream base consisting of cetyl alcohol, glyceryl stearate SE (nonionic), isopropyl myristate, mineral oil (and) lanolin alcohol, monobasic sodium phosphate, monoglyceride citrate, polyoxyl 40 stearate, polysorbate 60, propylene glycol, purified water, sorbitan monostearate, vegetable oil, butylated hydroxytoluene and citric acid.

NET WT 60 grams

APPROVED

Store at or below 25°C (77°F).
Keep tightly closed.
See crimp of tube for Lot No. and Exp. Date

X4374 R1/98

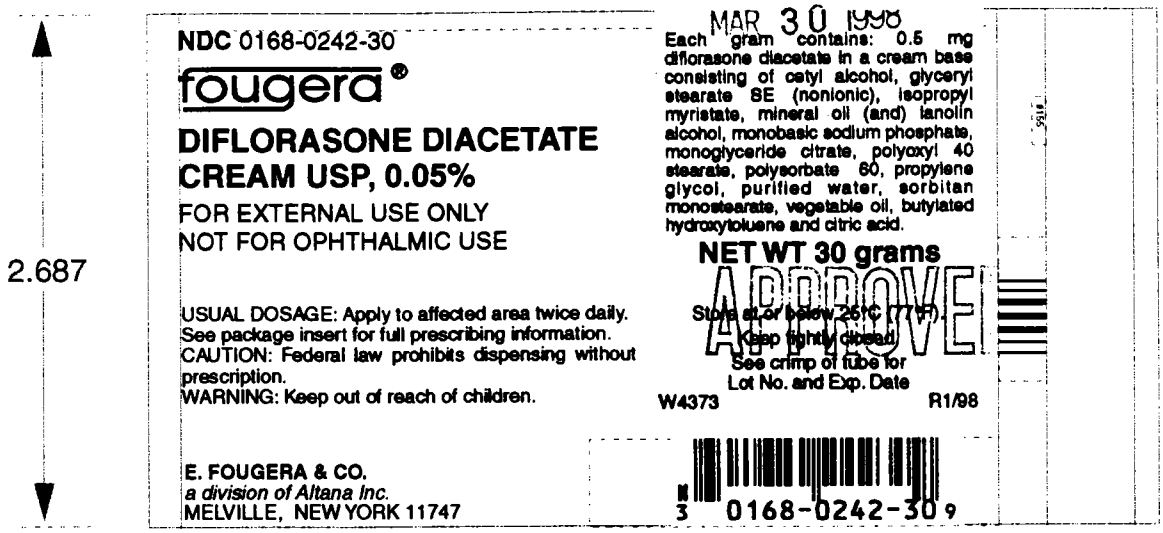
3 0168-0242-60 6

M 30

3.468

6.000

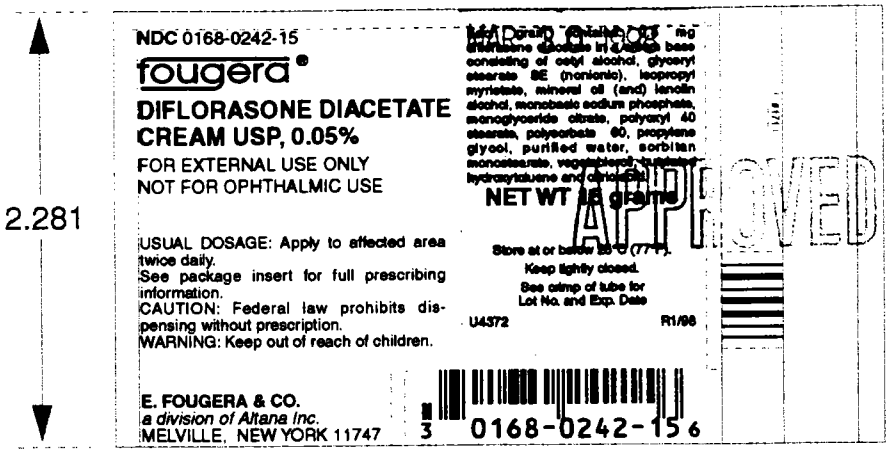
Item# X4374
Die Size:
Pharma # #198
Colors Black, Process Yellow



Item# W4373
Die Size:
Pharma # #155
Colors Black, Process Yellow

30 Grams Tube Template
Drawing #LB-513

Mango



Item# U4372
Die Size:
Pharma # #171
Colors Black, Process Yellow

4.000

15 grams Tube Temp.

Drawing LB-518

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75187

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-187

3. NAME AND ADDRESS OF APPLICANT

Altana Inc.
60 Baylis Rd.
Melville, NY 11747

4. LEGAL BASIS FOR SUBMISSION

The applicant certifies that in their opinion and to the best of their knowledge all listed patents claimed the reference listed drug have expired and no period of marketing exclusivity for the reference listed drug.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Diflorasone Diaetate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

9. AMENDMENTS AND OTHER DATES:

Original 8/20/97
Amendment 2/4/98
Amendment 3/6/98
Amendment 3/10/98

10. PHARMACOLOGICAL CATEGORY

Anti-inflammatory

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Cream

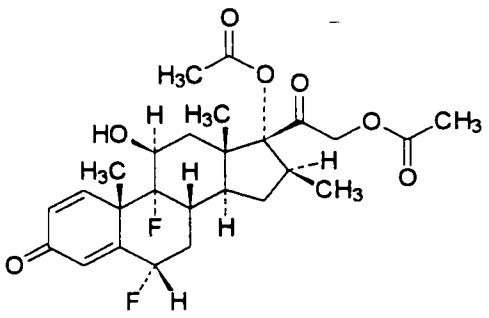
14. POTENCY

0.05%

15. CHEMICAL NAME AND STRUCTURE

Diflorasone Diacetate. Pregna-1,4-diene-3,20-dione, 17,21-bis(acetyloxy)-6,9-

difluoro-11-hydroxy-16-methyl-, (6α,11β,16β)-. $C_{26}H_{32}F_2O_7$. 494.54. 33564-31-7. Anti-inflammatory, Glucocortic. USP 23, page 508.



17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 3/10/98

Supervisor: Paul Schwartz, Ph.D.

cc: ANDA 75-187
Division File
Field Copy

Endorsements:

HFD-627/NNashed/3/10/98 3/12/98
HFD-627/PSchwartz/3/11/98
X:\NEW\FIRMSAM\ALTANA\LTRS&REV\75-187.2
F/t by: gp/3/11/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75187

BIOEQUIVALENCE REVIEW(S)

Diflorasone Diacetate

Topical cream, 0.05%
ANDA #75187
Reviewer: Gur J.P. Singh.
File #75187S.897

Altana

60 Baylis Road
Melville, NY 11747
Submission Dates:
August 20, 1997 and
January 22, 1998.

Review of a pilot dose-response study and a pharmacodynamic bioequivalence study

BACKGROUND

The firm has submitted an application on its Diflorasone Diacetate 0.05% cream. For this drug, there are two reference listed drugs (RLD's) in the orange book including Psorcon® 0.05% cream (Dermik) and Florone® 0.05% cream (Upjohn), and these products are rated "BX". The RLD used in studies reviewed hereafter is Psorcon® 0.05% cream (NDA #20205, approval date: 10/20/92), manufactured by Dermik Laboratories.

This application is based on the June 2, 1995, guidance for documentation of bioequivalence of topical dermatologic corticosteroids. This guidance recommended the use of dose duration method to study pharmacodynamic effects of topical corticosteroids manifested in the ability of these products to cause vasoconstriction of the skin micro-vasculature, leading to blanching of treated skin areas. In this method, vasoconstrictor responses of increasing durations of a formulation are measured as a function of time after treatment application. Because different dose durations represent different times for skin exposure to the test product, it has been assumed that increasing dose durations would results in correspondingly increasing amount of the drug available to penetrate the skin.

The guidance recommends the conduct of a pilot dose-response study and a pivotal bioequivalence study. The dose-duration to be used in the bioequivalence study comparing the test and the reference product is based on the *population* ED_{50} value obtained from the pilot dose-response study on the reference listed drug (RLD). The pivotal bioequivalence study also requires two calibrator dose durations D_1 and D_2, in addition to the ED_{50} value, where D_1 is approximately half of the bioequivalence study dose (ED_{50}) and D_2 is approximately 2 times the bioequivalence study dose.

The methodology employed to determine the bioequivalence of Altana's Diflorasone Diacetate 0.05% cream is consistent with the pilot-pivotal study concept recommended in the OGD guidance. Both pilot and pivotal studies are reviewed hereafter.

PILOT DOSE-RESPONSE STUDY

OBJECTIVE: To determine the population ED_{50} for the vasoconstrictor response of Diflorasone Diacetate 0.05% cream (Psorcon®0.05% cream) manufactured by Dermik Laboratories .

STUDY SITE, PERSONNEL AND DATES: The vasoconstrictor pilot study was performed at

Principal Investigator:
Dosing Date: August 24, 1996.

Study Protocol and Informed Consent: The protocol used for this study (#9628202, Date: 8/5/96) and Informed Consent were approved by the

SUBJECT SELECTION: Potential subjects were screened for vasoconstrictor response to the RLD, Psorcon^R 0.05% cream. One 10 μL portion of the RLD was applied to the upper arm above the forearm and left in place for approximately one hour. Skin blanching response was determined visually 7-8 hours after drug removal.

Fifteen (15) healthy, Caucasian, female volunteers screened above were enrolled for this study. The age of these subjects was in the range of 20-45 years (pp 991, vol 1.3). The weight range for these volunteers was 104-156 lbs. Subjects were selected based on acceptable medical history, negative pregnancy test, appropriate inclusion/exclusion criteria (pp 974-975, vol 1.3), and they signed informed consent.

STUDY DESIGN: The pilot study was conducted as a single period study. Diflorasone Diacetate cream used was Psorcon® 0.05% cream, lot #09022, expiry date: 10/97, manufactured by Dermik Laboratories .

The cream was applied on both arms. Eight (8) circular application sites (1.6 cm diameter) were designated on the flexor surface of the forearm between the wrist and the elbow. One untreated site was designated on each forearm. After baseline chromameter and visual readings, 10 μL portions of the cream were applied to assigned sites for 10, 20, 30 and 45 minutes, and 1, 1.5 and 3 hours prior to removal. All applications were removed at the same time. Thus the procedure used for drug application and removal was the *"Staggered application and synchronized removal"* method given in the June 2, 1995 guidance. Skin blanching was evaluated at 0, 2, 4, 6, 8, 10, 12, 20 and 24 hours after drug removal.

ASSESSMENT OF VASOCONSTRICTION: Skin blanching was determined based on chromameter and visual assessment of designated skin sites. Visual Scoring used the following rating scale:

SCORE	SKIN SURFACE CONDITION
0	No Pallor; no change from surrounding.
1	Mild Pallor; slight or indistinct outline of application site.
2	Moderate pallor; discernable outline of application site.
3	Intense pallor; clean, distinct outline of application site.

HOUSING AND MEALS: All subjects checked in at least 12 hours before dosing. Meals were served at traditional times. Caffeine and alcohol were restricted. Water was provided ***ad lib*** throughout the study. The subjects were released on day 2, approximately 27 hours after the first drug application. Subjects were instructed to avoid contact with water on their arms, and extreme temperature, and avoid strenuous exercise during the study. Tight clothing on the forearm was not permitted.

DATA ANALYSIS: The chromameter data were normalized for baseline values and changes in the color of the untreated skin as recommended in the guidance. AUEC's were calculated for 0-24 hours after drug removal using the trapezoidal rule. Similarly AUEC values were calculated based on visual scores. The pooled AUEC data as a function of the dose duration were fitted to the simple E_{max} model using PCNONLIN. Chromameter AUEC values used by the sponsor were found to be accurate with the exception that the firm multiplied all chromameter AUEC values by -1. AUEC's based on visual scores were also found to be accurate.

RESULTS: The firm used the software o determine ED_{50} values for the visual and chromameter data. is not a population modeling program. The technique used by the firm is known as the "naive pool" estimation of population ED_{50}, and this method does not keep track of the individual subject data. Therefore the population estimates based on this method may not represent the entire population.

The accurate way of determining population parameters is the "nonlinear mixed effect modeling" approach using population modeling computer programs. is one such program. The reviewer analyzed the chromameter- and visual-$AUEC_{0-24}$ data using this software. Pharmacodynamic parameter values based on sponsor's and reviewer's calculations are given below:

Data set	ED_{50}			E_{max}		
	Firm (A)	Rev. (B)	A/B	Firm (C)	Rev.(D)	C/D
Chroma-meter	69 (24)	154 (94)	0.44	-53 (9)	-69 (42)	0.77
Visual	27 (6)	32 (59)	0.84	48 (4)	49 (29)	0.98

Parametric data are given as mean (%CV). Coefficients of variation on reviewer's estimates are much larger than those reported by the firm because reviewer's analysis is based on mixed effect modeling which accounts for inter-subject as well as intra-subject variation in the pharmacodynamic response. Firm's analysis is based on the "naive-pool" method where all data in the pool are considered to originate from the same source (subject).

OGD guidance recommends assessment of bioequivalence primarily based on the chromameter data using a dose duration approximately equal to the population ED_{50}. The sponsor selected an ED_{50} value of 50 minutes for the pivotal study, and it was smaller than the *population* ED_{50} value based on chromameter of assessment of skin blanching. For determination of bioequivalence the use of a dose duration < population ED_{50} is acceptable because the comparison of test and reference products is made in the region of dose-response curve where sensitivity of the bioassay to variation in dose, as well as intra-subject variability in the pharmacodynamic response, may be higher, thereby making it harder for the test product to meet the bioequivalence interval (Singh et. al, *Pharm. Res.* **14**:S320, 1997). Therefore the dose duration of 50 minutes used in the pivotal bioequivalence study is acceptable.

PIVOTAL BIOEQUIVALENCE STUDY

OBJECTIVE: To study the relative vasoconstrictor effects of the test and reference Diflorasone Diacetate creams.

STUDY SITE, PERSONNEL AND DATES: The vasoconstrictor study was performed at the

Principal Investigator:

Dosing Dates:

Group 1 (Subject #1-25):	September 28, 1996
Group 2 (Subject #26-44):	October 19, 1996
Group 3 (Subject #44-54):	October 19, 1996

Study Protocol and Informed Consent: The protocol used for this study (#9628204, September 12, 1996) and Informed Consent were approved by the

SUBJECT SELECTION: Potential subjects were screened for vasoconstrictor response to the reference listed drug Psorcon® 0.05% cream as mentioned for the pilot study. All subjects were selected based on a demonstrated skin blanching response. Fifty nine (59) healthy, non-tobacco using female volunteers were enrolled for this study. Subject #45 dropped before dosing. The remaining 58 subjects (57 Caucasian, 1 Asian) were dosed. The age of these subjects was in the range of 18-50 years (pp 417-418, vol 1.2). The weight range for these volunteers was 104-165 lbs. These subjects were enrolled based on acceptable medical history, negative pregnancy test and a signed informed consent. Criteria used for subject exclusion were appropriate (pp 394-395, vol 1.2).

STUDY DESIGN: The pivotal study was conducted as a one-period/group study involving randomized applications of the test formulations to both arms along with the replicate applications of the calibrator doses (D_1 and D_2) of the reference product. There were two untreated control sites on each arm. The treatment randomization provided complementary applications on left and right arm as given below:

ANTECUBITAL FOSSA

Right Arm		Left Arm	
Site	Treatment	Site	Treatment
8	D2	16	D1
7	REF	15	Test
6	Untreated	14	Untreated
5	Test	13	REF
4	Untreated	12	Untreated
3	D1	11	D2
2	Test	10	REF
1	REF	9	Test

WRIST

Where:

Test: Diflorasone Diacetate 0.05% cream, Altana, (Lot #8851, Lot size: expiry date: not known) applied for dose duration of 50 minutes.

REF: Psorcon® topical cream 0.05% (Lot #09022, expiry date: 10/97) manufactured by Dermik Laboratories, applied for dose duration of 50 minutes.

D_1: Psorcon® topical cream 0.05% (Lot #09022, expiry date: 10/97) manufactured by Dermik Laboratories, applied for dose duration of 25 minutes.

D_2: Psorcon® topical cream 0.05% (Lot #09022, expiry date: 10/97) manufactured by Dermik Laboratories, applied for dose duration of 100 minutes

TREATMENT ADMINISTRATION: Subjects were treated in three groups. The forearm of each subject was washed with mild soap and gently dried within two hours prior to dosing. Eight (8) circular application sites (approximate diameter 1.6 cm) were designated on the flexor surface of each arm. Using a 250 μL Hamilton syringe, 10 μL application of active drug were applied to six (6) sites on each arm as shown in the schematics above. The actual randomization for various treatments is given on pages 419-421 (vol 1.2). The products were evenly spread within each site using the conical tip of a 1.5 mL polypropylene microcentrifuge tube. All sites were kept unoccluded throughout the study.

The application of active treatments was staggered. Consistent with the pilot study, all treatments were removed at the same time following the *"staggered application and synchronized removal"* scheme recommended in the June 2, 1995, OGD guidance.

At the end of the treatment period, all sites (including the untreated spots) were gently wiped several times with a cotton ball. Skin blanching assessments were performed at 0, 2, 4, 6, 8, 10, 12, 21 and 24 hours after drug removal.

HOUSING AND MEALS: Same as that given for the pilot study.

ASSESSMENT OF VASOCONSTRICTION: Same as that given for the pilot study.

METHOD VALIDATION: Prior to the pivotal study, precision (%CV) for chromameter operators was evaluated from replicate evaluations of five readings/site taken at least three minutes apart. For this method validation four subjects were studied, and four untreated sites on each arm of these subjects were evaluated. Results of method validation are summarized on page 609-658 (vol 1.2). Intra-site %CV was in the range of 5.4%-6.2%, and inter-site %CV was in the range of 12.1%-12.9%.

DATA ANALYSIS: Chromameter data was transformed and AUEC's were calculated as mentioned in the pilot study. The $AUEC_{0-24}$ values for visual assessment of skin blanching were calculated directly from the raw blanching scores.

The ratio of mean $AUEC_{0-24}$ value (average of left and right arm values) for D_2/D_1 was calculated for each subject. Subjects whose D_2/D_1 ratios were ≥ 1.25 were considered to be "evaluable subjects" (see below) and included in the statistical analyses.

The $AUEC_{0-24}$ data for evaluable subjects, based on visual and chromameter readings, were used to calculate the 90% confidence intervals using Locke's method, as recommended in the OGD guidance.

RESULTS

Clinical Conduct of the Study: All 58 subjects dosed in this study completed the two days of evaluation. No drug related adverse event was reported in this study. The firm has reported visual scores data for all 58 subjects. However, chromameter data are presented for 56 subjects, excluding subjects #34 and #37. Based on the telephone amendment of January 22, 1998, chromameter evaluations for subjects 34 and 37 were performed, but they had incomplete data sets with one value missing for each subject. Therefore these two subjects' data were not included in analyses.

Accuracy of Pharmacodynamic Metric Data: Vasoconstrictor responses of test and reference products were compared based on the chromameter assessment and visual scoring. The reviewer has verified the adjustment of the chromameter raw data for the baseline and changes that occurred in the untreated skin. The adjusted data were used for calculation of the pharmacodynamic metric, $AUEC_{0-24}$. For the presentation of chromameter AUEC data the sponsor reversed the sign from negative to positive. The reversal of sign, in this manner, poses problems in selection of "evaluable subjects" in the manner described in the June 2, 1995, guidance. Therefore, all chromameter AUEC were multiplied by "-1". The resulting $AUEC_{0-24}$ data showed values identical to those calculated by the reviewer (see table 1, attachment). The visual-score AUEC's reported by the sponsor for a number subjects were found to be inaccurate, because the reported AUEC values were not adjusted for vasoconstriction at untreated sites (see table 2, attachment). Therefore, all bioequivalence data presented in this review are based on reviewer's calculations.

Evaluable Subjects: Based on the OGD guidance "evaluable subjects" are those which exhibit AUEC-D_2/AUEC-D_1 ratio of ≥ 1.25, and this guidance recommends the inclusion of only evaluable subjects' data in statistical analyses for documentation of bioequivalence. There were 29 and 39 such subjects based on chromameter and visual assessment, respectively (Tables 3 and 4, attachment). There were some subjects which qualified for bioequivalence evaluation based on both methods of assessment (visual and chromameter) whereas the others were qualified by one or the other method.

Based on the chromameter data, the number of "evaluable subjects" determined by the sponsor were 35, which included 6 subjects not selected by the reviewer. The selection of these six subjects (#7,

8, 14, 17, 28 and 53, pp 604, vol 1.2) by the sponsor is not consistent with the OGD guidance. Therefore bioequivalence testing is based on data from 29 subjects. Based on visual scores data the sponsor qualified 45 subjects for bioequivalence comparisons, instead of 39 determined by the reviewer. The discrepancy between these numbers is because of erroneous AUEC values used by the sponsor and inappropriate criteria for selection of evaluable subjects. The results of bioequivalence evaluation are based on "evaluable subjects" determined by the reviewer.

With regard to the steepness of the dose response for this study, based on all 56 subjects' chromameter data, mean AUEC-D_2 was 106% greater than the mean AUEC-D_1. The difference between the pharmacodynamic responses of D_1 and D_2 based on visual scores was 109%.

Evaluation of Bioequivalence: .

$AUEC_{0-24}$ data for chromameter and visual assessment of skin blanching are given in tables 5 and 6 (attachment). The presence of both positive and negative AUEC values in the chromameter data set precludes the use of log-transformation and the standard two-sided t-test procedure for calculation of the 90% confidence intervals. Instead, the OGD guidance recommends the use of Locke's method *(J. Pharmac. Biopharm.*, 12:649-65, 1984).

The bioequivalence data based on reviewer's calculation of confidence intervals using $AUEC_{0-24}$ data for evaluable subjects and Locke's method are given below:

Assessment Method	Test (A)	Reference (B)	A/B	90% CI
Chromameter (n = 29)	**-16.63 (60)**	**-16.97 (59)**	**0.92**	**85-112**
Visual (n = 39)	**22.01 (49)**	**22.04 (49)**	**1.00**	**93-107**

Data are given as Mean(%CV)

Based on both chromameter and visual assessments of skin blanching, 90% confidence intervals were within the acceptable limit of 80-125%.

PRODUCT COMPOSITION (NOT TO BE RELEASED UNDER FOI):

Compositions of Altana's Diflorasone Diacetate 0.05% cream and Psorcon® 0.05% Cream (Reference product, NDA 20205). Ingredient strengths are given as percent concentrations in finished products.

Ingredient	TEST	REF
Diflorasone Diacetate	0.05%	0.05%
Water, USP		
Propylene Glycol		
Mineral Oil & Lanolin Alcohols[a]		
Glyceryl Stearate (nonioinic)		
Isopropyl Myristate[b]		
Polysorbate 60		
Sorbitan Monostearate		
Polyoxyl 40 Stearate		
Cetyl Alcohol		
Sodium Phosphate, Monobasic		
Vegetable Oil		
Monoglyceride Citrate		
Butylated Hydroxytoluene		
Citric Acid (anhydrous)		

PNG: Potence not given. [a] *For the RLD, Mineral Oil & Lanolin Alcohols are listed separately; their potencies are not given.* [b] *The reference product contains Myristyl Alcohol*

The RLD composition listed above is based on the CDER database (COMIS). All ingredients listed for the test product have been previously used for the same route of administration [*Inactive Ingredient Guide (January 1996)*].

IN VITRO RELEASE PROFILES

The sponsor did not submit *in vitro* release data for its Diflorasone Diacetate 0.05% cream. The June 2, 1995, OGD guidance does not require *in vitro* release data to support product approval. However the guidance states that " Following future recommendations of the Scale-Up and Post Approval Changes for Semisolid (SUPAC-SS), OGD may recommend the submission of *in vitro* release data to support waiver of *in vivo* bioequivalence of the lower strength(s) of topical corticosteroid products....".

COMMENTS:

1. The sponsor performed a pilot dose-response study based on the OGD guidance. Based on the "naive pool" analysis of the dose response data (chromameter), it calculated an ED_{50} of approximately 69 minutes. However the naive pool analysis may not provide an ED_{50} representative of the population (Singh et. al, *Pharm. Res.* **14**:S320, 1997). Therefore, the reviewer calculated population ED_{50} using the "nonlinear mixed effect modeling" approach. The population ED_{50} values for the chromameter was found to be 154 minutes.

   Bioequivalence data used for product evaluation in the pivotal study are based on an ED_{50} of 50 minutes. For the reasons given in the review of the pilot study, a dose duration of 50 minutes for the comparison of test and reference products in the pivotal bioequivalence study was found to be acceptable.

2. Based on both the chromameter and visual evaluation of skin blanching, 90% confidence intervals comparing the test and the reference products were within the acceptable limit of 80-125%.

3. Based on both chromameter and visual assessments of skin blanching, the test product is bioequivalent to the reference product.

RECOMMENDATIONS

1. The *in vivo* bioequivalence study conducted by Altana comparing its Diflorasone Diacetate 0.05% cream (lot #8851) to the reference product, Psorcon^R 0.05% cream (lot #09022) has been found to be acceptable to the Division of Bioequivalence. The results of this vasoconstrictor study demonstrate that Altana's Diflorasone Diacetate 0.05% cream is bioequivalent to the reference product, Psorcon^R 0.05% cream manufactured by Dermik Laboratories .

2. The sponsor should be informed that AUEC values based on visual scores should be corrected for skin blanching at untreated sites, if any of these sites are assigned nonzero scores. Visual AUEC values submitted in this application were corrected by the reviewer; all future submissions should report correct AUEC values.

Gur J.P. Singh, Ph.D.
Review branch II
Division of Bioequivalence.

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR: _____ 1/27/1998

CONCUR: _____ DATE 1/30/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence.

GJP SINGH 1/22/98 75187S.897
cc. ANDA # 75187, original, HFD-650 (Division Director), HFD-630 (OGD), HFC-130 (Jallen), HFD-600 (Hare), HFD-655 (Nerurkar, Singh), Drug file, Division file.

ATTACHMENTS

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-187 APPLICANT: Altana

DRUG PRODUCT: Diflorasone Diacetate cream, 0.05%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that AUEC values based on visual scores should be corrected for skin blanching at untreated sites, if any of these sites are assigned nonzero scores. Visual AUEC values submitted in this application were corrected by the reviewer; all future submissions should report correct AUEC values.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional BIOEQUIVALENCY information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

The above comments were transmitted to the firm. Ms Carmen confirmed receipt 2/3/98.

3/11/98

AUEC-D2/AUEC-D1 ratios based on chromameter data and reviewer's calculations (ANDA #75187)

SUB	AUEC (0-24) D1	D2	D2/D1	SUB	AUEC (0-24) D1	D2	D2/D1
1				31			
2				32			
3				33			
4				35			
5				36			
6				38			
7				39			
8				40			
9				41			
10				42			
11				43			
12				44			
13				46			
14				47			
15				48			
16				49			
17				50			
18				51			
19				52			
20				53			
21				54			
22				55			
23				56			
24				57			
25				58			
26				59			
27							
28							
29							
30							

Mean	-12.78	-26.40
%CV	100	53
n	56	56
Mean	-13.02	-30.99
%CV	63	44
n	29	29

The individual subject AUEC(0-24) data represent average value of the left and right arm replicates.

Highlighted cells indicate evaluable subjects (n=29) with D2/D1 ratio of 1.25 or greater.

AUEC-D2/AUEC-D1 ratios based on visual scores data and reviewer's calculations (ANDA #75187)

SUB	AUEC (0-24) D1	D2	D2/D1	SUB	AUEC (0-24) D1	D2	D2/D1
1				31			
2				32			
3				33			
4				34			
5				35			
6				36			
7				37			
8				38			
9				39			
10				40			
11				41			
12				42			
13				43			
14				44			
15				46			
16				47			
17				48			
18				49			
19				50			
20				51			
21				52			
22				53			
23				54			
24				55			
25				56			
26				57			
27				58			
28				59			
29							
30							

Mean	14.39	30.08
%CV	93	39
n	58	58
Mean	13.01	32.09
%CV	64	30
n	39	39

The individual subject AUEC(0-24) data represent average value of the left and right arm replicates.

Highlighted cells indicate evaluable subjects (n=39) with D2/D1 ratio of 1.25 or greater.

Table 5: AUEC (0-24) for test and reference products based on chromameter data and reviewer's calculations (ANDA #75187)

AUEC (0-24)

All Subjects								Evaluable Subjects			
SUB	TEST	REF	TEST/REF	SUB	TEST	REF	TEST/REF	SUB	TEST	REF	TEST/REF
1				31				1			
2				32				3			
3				33				4			
4				35				6			
5				36				9			
6				38				10			
7				39				13			
8				40				15			
9				41				16			
10				42				19			
11				43				20			
12				44				21			
13				46				22			
14				47				24			
15				48				25			
16				49				26			
17				50				35			
18				51				39			
19				52				40			
20				53				42			
21				54				43			
22				55				46			
23				56				49			
24				57				52			
25				58				54			
26				59				55			
27								57			
28				Mean	-16.37	-15.61		58			
29				%CV	65	67		59			
30				n	56	56					
								Mean	-16.63	-16.97	
								%CV	60	59	
								n	29	29	

The individual subject AUEC(0-24) data represent average values of left and right arm replicates.

Shaded cells at the left indicate test and reference product AUEC's for "evaluable subjects (right hand data set)" used for bioequivalence determination, as these subjects (n= 29) showed D1/D1 ratios of 1.25 or greater.

Table 6: AUEC (0-24) for test and reference products based on visual scores data and reviewer's calculations (ANDA #75187)

AUEC (0-24)

All Subjects								Evaluable Subjects			
SUB	TEST	REF	TEST/REF	SUB	TEST	REF	TEST/REF	SUB	TEST	REF	TEST/REF
1				31				1			
2				32				3			
3				33				7			
4				34				9			
5				35				10			
6				36				12			
7				37				13			
8				38				18			
9				39				20			
10				40				21			
11				41				22			
12				42				24			
13				43				25			
14				44				28			
15				46				29			
16				47				30			
17				48				32			
18				49				33			
19				50				34			
20				51				35			
21				52				37			
22				53				39			
23				54				40			
24				55				41			
25				56				42			
26				57				43			
27				58				44			
28				59				46			
29								47			
30								49			
				Mean	22.00	22.45		50			
				%CV	59	59		51			
				n	58	58		52			
								53			
								54			
								56			
								57			
								58			
								59			
								Mean	22.01	22.04	
								%CV	49	49	
								n	39	39	

The individual subject AUEC(0-24) data represent average values of left and right arm replicates.

Shaded cells at the left indicate test and reference product AUEC's for "evaluable subjects (right hand data set)"used for bioequivalence determination, as these subjects (n= 39) showed D2/D1 ratios of 1.25 or greater.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75187

ADMINISTRATIVE DOCUMENTS

APPROVAL PACKAGE SUMMARY FOR 75-187

ANDA: 75-187

FIRM: Altana Inc.

DRUG: Diflorasone Diacetate

DOSAGE: Cream

STRENGTH: 0.05%

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 1/8/98

BIO STUDY/BIOEQUIVALENCE STATUS: bio is satisfactory 1/27/98

METHOD VALIDATION: The drug is compendial - methods verification is acceptable 11/13/97

STABILITY: The firm has submitted satisfactory 3 months accelerated stability data at 40°C/75%RH, and 12 months room temperature at 25°C/60%RH for 15 mL, 30 mL and 60 mL packaging sizes.

LABELING REVIEW STATUS: Labeling is satisfactory 2/18/98

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has provided the master formula and manufacturing procedure for the maximum batch and copy of the exhibit batch lot #8851 for The firm will be using the same drug substance manufacturer The DMF is satisfactory, and same equipment and manufacturing procedure.

COMMENTS: The Application is Approvable.

3/12/98

REVIEWER: Nashed E. Nashed, Ph.D. DATE: 3/10/98

SUPERVISOR: Paul Schwartz, Ph.D.

3/11/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75187

CORRESPONDENCE

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-454-6389 BYK GULDEN PHARMA GROUP

Federal Express

505(j) # OK 9/8/97

August 20, 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Re: Original Submission
Abbreviated New Drug Application
Diflorasone Diacetate Cream USP, 0.05%

Dear Sir or Madam:

Pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act and in accordance with the provisions of the Regulations contained in 21 CFR §314.94, Altana Inc., is submitting this Abbreviated New Drug Application to market a new drug, Diflorasone Diacetate Cream USP, 0.05%.

The reference listed drug that is the basis for this submission is psorcon® (diflorasone diacetate cream) 0.05% (NDA 20-205), manufactured by Dermik Laboratories, Inc. The proposed drug, Diflorasone Diacetate Cream USP, 0.05%, contains the same active ingredient in the same strength and dosage form, has the same indications and usage, and route of administration as the reference listed drug.

The exhibit batch (#8851) included in this application was fully packaged utilizing the 15 gram, 30 gram, and 60 gram presentations for which approval is currently requested. The number of units filled of each package size and the disposition of any remaining bulk product are reconciled in the exhibit batch record.

Included in this five (5) volume submission, along with Form FDA 356h, is the required Patent Certification and Exclusivity statements, draft Labeling, Bioequivalence Studies, full Components and Composition statements, Raw Materials controls, description of the

Manufacturing Facilities, Manufacturing and Processing instructions, In-process Controls, Filling and Packaging procedures, information on the Container/Closure System, controls for the Finished Dosage Form, Analytical Methods, Finished Dosage Form Stability, Environmental Impact Analysis statement, Certification Requirements of the Generic Drug Enforcement Act of 1992, and the Sterile Process validation package.

All regulatory correspondences related to this Abbreviated New Drug Application should be addressed to:

Virginia Carman
Associate Director
Regulatory Affairs
Altana Inc.
60 Baylis Road
Melville, NY 11747
Tel. No. (516) 454-7677 Ext. 2091
Fax No. (516) 454-6389

A certified copy of this application (consisting of volumes 1.1, 1.4 & 1.5 and a copy of the Methods Validation package) is being sent to the New York District Office under separate cover.

We trust that this submission will meet with your approval. Please advise us if you require any additional information.

Sincerely,
Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

Enclosures

VC/ab

C:\DIFLORA\COVER.LTR

3/11/98

ALTANA

60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-454-6389 BYK GULDEN PHARMA GROUP

Federal Express

March 10, 1998

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry 1
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2 Room 286
7500 Standish Place
Rockville, MD 20855-2773

NDA CHAP ASSIGNMENT
N/FA

Re: ANDA 75-187
Diflorasone Diacetate Cream USP, 0.05%

Dear Dr. Patel:

Reference is made to our original abbreviated New Drug Application submitted, August 0, 1997 as well as our telefax amendment of February 4, 1998.

Reference is also made to telephone conference between Mr. Joseph Buccine of the OGD nd Mr. Dave Pearce and Ms. Virginia Carman of Altana Inc. concerning our proposed pecifications.

We were requested to revise the pH specifications. The limits were revised from for all specifications.

his information was also telefaxed to the office on this date.

there are any further questions, please do not hesitate to contact me at (516) 454-7677 t. 2091.

Sincerely,

ALTANA INC.

Patricia Sell for/

Virginia Carman
Associate Director
Regulatory Affairs

Dear

RECEIVED
MAR 1 1 1998
GENERIC DRUGS

ALTANA

-454-7677 Fax: 516-454-6389 BYK GULDEN PHARMA GROUP

March 6, 1998

Rashmikant M. Patel, Ph.D
Director
Division of Chemistry 1
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2 Room 286
7500 Standish Place
Rockville, Md 20855-2773

NEW CORRESP

RE: ANDA 75-187
Diflorasone Diacetate Cream USP, 0.05%

Dear Dr. Patel:

Reference is made to our original abbreviated New Drug Application submitted August 20, 1997 as well as our telefax amendment of February 4, 1998.

Reference is also made to telephone conference between Mr. Joseph Buccine of the OGD and Mr. Dave Pearce and Ms. Virginia Carman of Altana Inc. concerning our proposed stability specifications.

We were requested to revise the limits of the degradation products in our stability specifications. The individual degradation product specification was revised from
the total from

This information was also telefaxed to the office in this date.

If there are any further questions, please do not hesitate to contact me at (516) 454-7677 ext. 2091.

Sincerely,
Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

VC/lb
B:\ANDA7518.WPD

RECEIVED
MAR 9 1998
GENERIC DRUGS

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-454-6389 BYK GULDEN PHARMA GROUP

FEDERAL EXPRESS

February 4, 1998

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry 1
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2, Room 286
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-187 FACSIMILE AMENDMENT
Diflorasone Diacetate Cream USP, 0.05%

Dear Dr. Patel:

Reference is made to our original Abbreviated New Drug Application of August 20, 1997, as well as your telefax of January 8, 1998 in which several deficiencies were noted.

We also refer to your telefax of February 3, 1998 concerning our bioequivalence study.

We wish to respond to each of the concerns noted in your January 8, 1998 telefax as follows:

A. Deficiencies

1. Comment

Please revise your drug substance specifications to include specifications and limits for residual solvents particle size, and for individual and total impurities.

Response

Revised drug product specifications which have been revised to include residual solvent specifications and limits, particle size, as well as individual and total impurities may be found in Attachment 1.

2. Comment

Please tighten your limits for degradation products based on your data for the finished product and stability.

Response

Revised finished product specifications, in which the limits for degradation products have been tightened from
with the total remaining at are included in Attachment 2. Revised stability specifications in which the limits for single degradation products were tightened from and the total revised from
may be found in Attachment 3 .

3. Comment

Please tighten your specifications for in-process, release of finished product and stability regarding the limits for pH and viscosity.

Response

Revised in process specifications which included tightening of the pH and viscosity limits may be found in Attachment 4.
Revised Finished Product, and Stability specifications can be found in Attachments 2 and 3 respectively.

4. Comment

Please revise your limits for the total aerobic microbial count to not more than for the release of finished product and stability.

Response

The finished product, and stability specifications have been revised to include the lower specification of for the total aerobic microbial count. This information can be found in Attachments 2 and 3.

5. Comment

Please explain the difference in the limits of viscosity and particle size on p. 1901 and p. 1905.

Response

The specifications used to release the material were the initial specifications written for this product (FP 0242.00). Since that time additional analytical data have become available which has allowed us to better define the specifications. In this case the limits of viscosity have been shifted and tightened, and the particle size slightly widened.
The finished product specification has since been tightened again for viscosity as a response to your telefax. Please see Attachment 2 for the revised finished product specifications.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response.

As requested:

Altana Inc. acknowledges that the firms referenced in our application regarding manufacturing or testing should be in compliance at the time of approval.

We also agree that the USP methods are the regulatory methods and will prevail in the event of a dispute.

Labeling Deficiencies:

Comment

1. CONTAINER (15 g, 30 g, 60 g)

   a. Please ensure that the established name and strength is the most prominent information appearing on the label.

   b. Revise to read, "FOR EXTERNAL USE ONLY" rather than "FOR DERMATOLOGIC USE ONLY".

   C. Revise the "USUAL DOSAGE" statement to read, Apply to affected area twice daily. See package...

Response

Final Printed Container labeling which incorporates all of the above revisions may be found in Attachment 5.

Comment

2. CARTON (15 g, 30 g, 60 g)

   See CONTAINER comments.

Response

Final Printed Carton labeling which contains the requested revisions may be found in Attachment 6.

3. INSERT

a. GENERAL COMMENT

Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when sentence structure warrants, the USAN name stands alone as on labels or the title of the package insert.

b. DESCRIPTION

Revise the first sentence of the ultimate paragraph to delete "USP".

c. CONTRAINDICATIONS

Revise to delete "USP", 0.05%".

d. PRECAUTIONS

i. General

Revise the second sentence of the third paragraph to delete the use of "USP" with the established name.

ii. Carcinogenesis, Mutagenesis and Impairment of Fertility.

Revise to delete "and" from the subsection heading.

iii. Pediatric Patients

Revise to replace "children" with pediatric patients". (5 places)

Please revise your labels and labeling, as instructed above, and submit in final print.

Response

Final printed insert labeling which incorporates the FDA's requested changes is included in Attachment 7.

A side-by-side comparison of our revised labeling with that of our last submission is included as follows:

Container -	Attachment	8
Carton -	Attachment	9
Insert -	Attachment	10

We acknowledge that the Agency reserves the right to request further changes in the labeling based upon further review of our application.

We also acknowledge that the bioequivalency comments provided in your February 3, 1998 communication are preliminary and may be revised as a result of the review of the entire application. We are aware that additional data may be required.

Please note that a field copy of this amendment has been submitted to the local district office.

If there is any further information required, please contact me (516) 454-7677 ext. 2091.

Sincerely,
Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

Enclosure

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