CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-905

Approval Letter

ANDA 74-905

AUG 26 1997

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

Dear Madam:

This refers to your abbreviated new drug application dated May 23, 1996, submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluocinonide Ointment USP, 0.05%.

Reference is also made to your amendments dated August 5, 1996; and February 26, March 5, April 4, July 14, and August 6, 1997.

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 that your Fluocinonide Ointment USP, 0.05% is bioequivalent and, therefore, therapeutically equivalent, to the listed drug (Lidex® Ointment 0.05% of Syntex USA, 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,

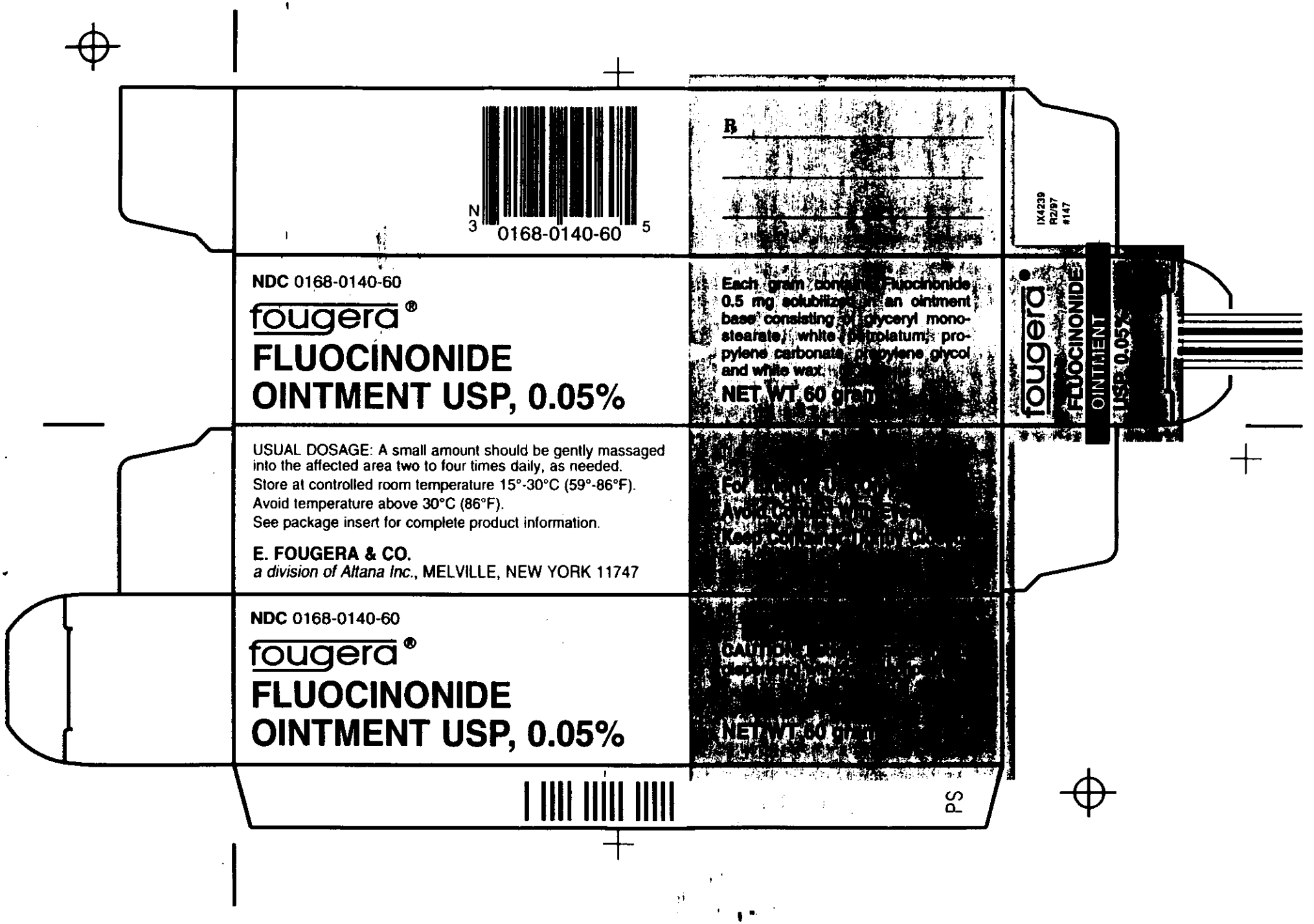
/S/ 4/29/11

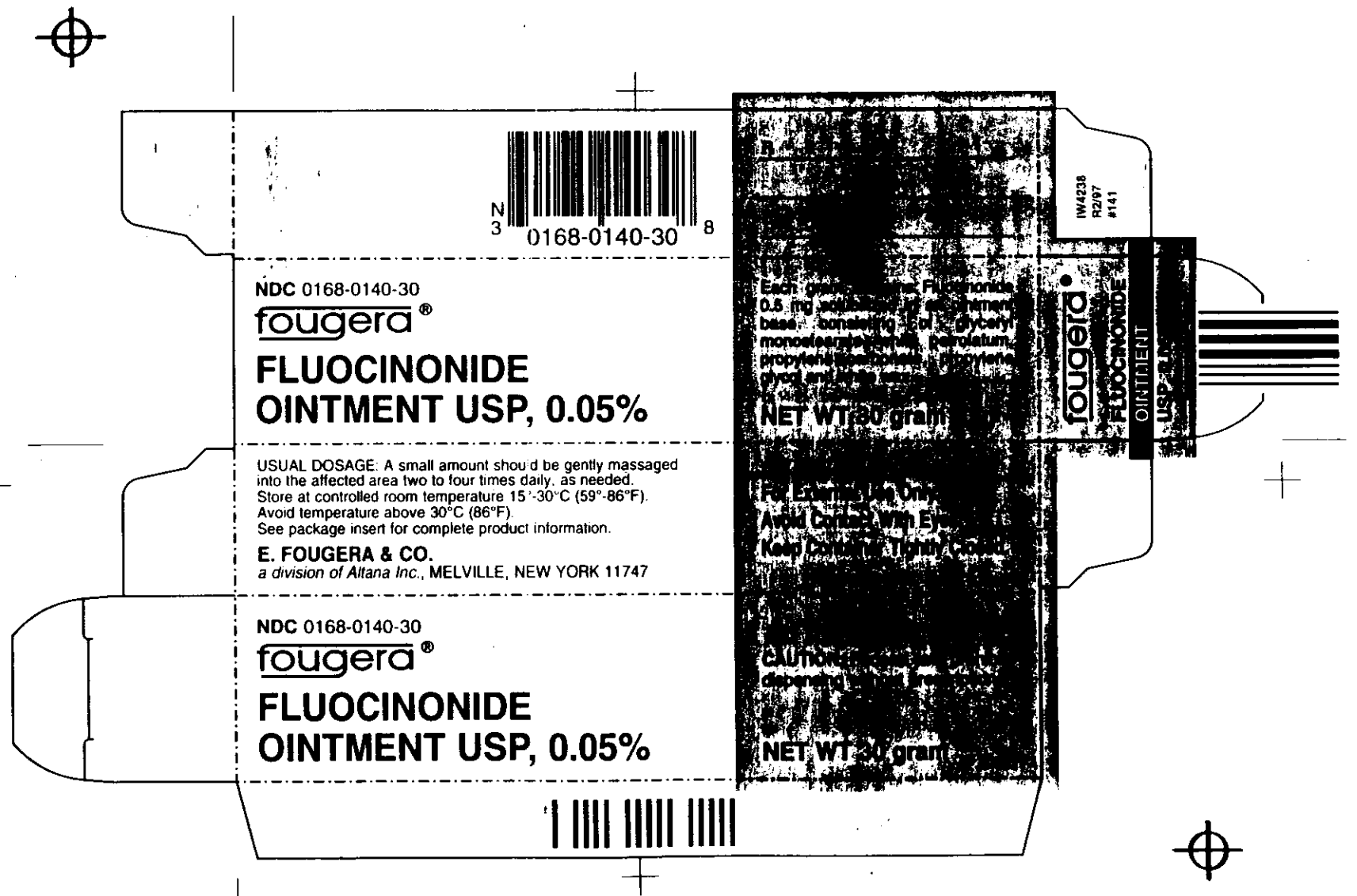
Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-905

FINAL PRINTED LABELING


N
3 0168-0140-60 5
NDC 0168-0140-60
fougera®
FLUOCINONIDE
OINTMENT USP, 0.05%
USUAL DOSAGE: A small amount should be gently massaged into the affected area two to four times daily, as needed.
Store at controlled room temperature 15°-30°C (59°-86°F).
Avoid temperature above 30°C (86°F).
See package insert for complete product information.
E. FOUGERA & CO.
a division of Altana Inc., MELVILLE, NEW YORK 11747
Each gram contains: Fluocinonide 0.5 mg solubilized in an ointment base consisting of glyceryl monostearate, white petrolatum, propylene carbonate, propylene glycol and white wax.
NET WT 60 gram
fougera
FLUOCINONIDE
OINTMENT
USP 0.05%
IX4239
R2/97
#147
NDC 0168-0140-60
fougera®
FLUOCINONIDE
OINTMENT USP, 0.05%
PS


N
3
0168-0140-30
8
NDC 0168-0140-30
fougera®
FLUOCINONIDE
OINTMENT USP, 0.05%
USUAL DOSAGE: A small amount should be gently massaged into the affected area two to four times daily, as needed.
Store at controlled room temperature 15°-30°C (59°-86°F).
Avoid temperature above 30°C (86°F).
See package insert for complete product information.
E. FOUGERA & CO.
a division of Altana Inc., MELVILLE, NEW YORK 11747
NDC 0168-0140-30
fougera®
FLUOCINONIDE
OINTMENT USP, 0.05%
NET WT 30 gram
IW4238
R2/97
#141
fougera
FLUOCINONIDE
OINTMENT
USP 0.05%

SHOULDER

TUBE LENGTH 6"

B.M. 1/8"

OPEN END

3 15/32 CIRCUMFERENCE

NDC 0168-0140-60

fougera®

FLUOCINONIDE OINTMENT USP, 0.05%

For Topical Use Only
Not For Ophthalmic Use

USUAL DOSAGE: A small amount should be gently massaged into the affected area two to four times daily, as needed.

See package insert for complete product information.

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

Each gram contains: Fluocinonide 0.5 mg solubilized in an ointment base consisting of glyceryl monostearate, white petrolatum, propylene carbonate, propylene glycol and white wax.
CAUTION: Federal law prohibits dispensing without prescription.

NET WT 60 grams

FOR EXTERNAL USE ONLY.
AVOID CONTACT WITH EYES.
Store at controlled room temperature 15°-30°C (59°-86°F).
Avoid temperature above 30°C (86°F).
See crimp of tube for Exp. Date and Lot Number.

R2/97 **X4239**

N 3 0168-0140-60 5

COPY START 1/8"

SHOULDER

TUBE LENGTH 5 1/4"

B.M. 1/8"

OPEN END

2 11/16 CIRCUMFERENCE

NDC 0168-0140-30

fougera®

FLUOCINONIDE OINTMENT USP, 0.05%

For Topical Use Only
Not For Ophthalmic Use

USUAL DOSAGE: A small amount should be gently massaged into the affected area two to four times daily, as needed.

See package insert for complete product information.

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

Each gram contains: Fluocinonide 0.5 mg solubilized in an ointment base consisting of glyceryl monostearate, white petrolatum, propylene carbonate, propylene glycol and white wax.
CAUTION: Federal law prohibits dispensing without prescription.

NET WT 30 grams

FOR EXTERNAL USE ONLY.
AVOID CONTACT WITH EYES.
Store at controlled room temperature 15°-30°C (59°-86°F). Avoid temperature above 30°C (86°F).
See crimp of tube for Exp. Date and Lot Number.

R2/97 W4238

N 3 0168-0140-30 8

AUG 26 [illegible]

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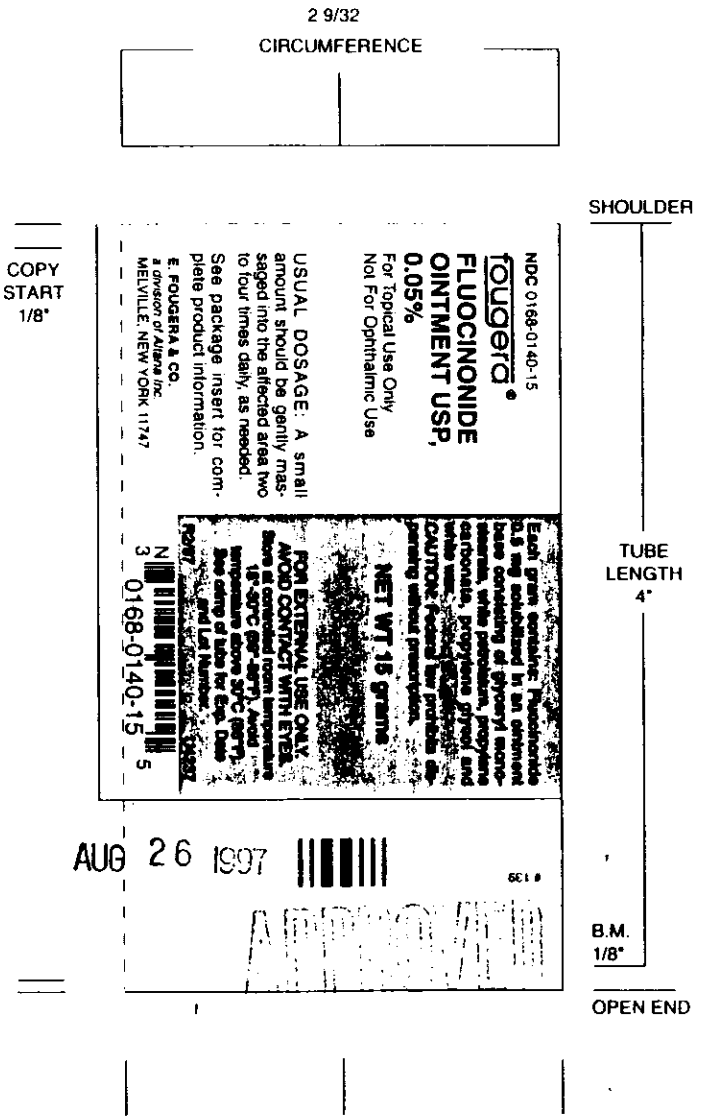
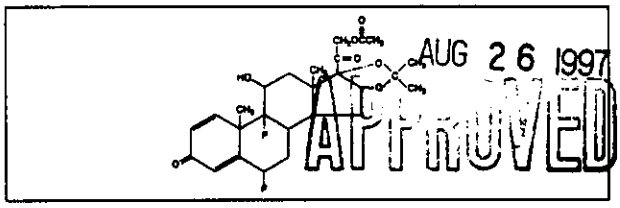

2 9/32
CIRCUMFERENCE
SHOULDER
COPY START 1/8"
NDC 0168-0140-15
fougera®
FLUOCINONIDE OINTMENT USP, 0.05%
For Topical Use Only
Not For Ophthalmic Use
NET WT 15 grams
USUAL DOSAGE: A small amount should be gently massaged into the affected area two to four times daily, as needed.
See package insert for complete product information.
E. FOUGERA & CO.
a division of Altana Inc.
MELVILLE, NEW YORK 11747
0168-0140-15
AUG 26 1997
TUBE LENGTH 4"
B.M. 1/8"
OPEN END

fougera®

FLUOCINONIDE OINTMENT USP, 0.05%

DESCRIPTION: Fluocinonide Ointment USP, 0.05% is intended for topical administration. The active component is the corticosteroid Fluocinonide, which is the 21-acetate ester of fluocinolone acetonide and has the chemical name pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-6,9-difluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-, (6α,11β,16α)-. It has a molecular formula of $C_{26}H_{32}F_2O_7$ and a molecular weight of 494.53. It has the following structural formula:



Each gram of Fluocinonide Ointment USP, 0.05% contains fluocinonide 0.5 mg in a specially formulated ointment base consisting of glyceryl monostearate, white petrolatum, propylene carbonate, propylene glycol and white wax. It provides the occlusive and emollient effects desirable in an ointment.
In this formulation, the active ingredient is totally in solution.

CLINICAL PHARMCOLOGY: 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. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

INDICATIONS AND USAGE: Fluocinonide Ointment USP, 0.05% is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS: Topical corticosteroids 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 area, 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.
As with any topical corticosteroid product, prolonged use may produce atrophy of the skin and subcutaneous tissues. When used on intertriginous or flexor areas, or on the face, this may occur even with short-term use.

(over)

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial 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 the Patient: 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 a 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. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

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 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 children receiving topical corticosteroids. Manifestations of adrenal suppression in children 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 children 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 are reported infrequently 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: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria.

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

DOSAGE AND ADMINISTRATION: Fluocinonide Ointment USP, 0.05% is generally applied to the affected area as a thin film from two or four times daily depending on the severity 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 instituted.

HOW SUPPLIED: Fluocinonide Ointment USP, 0.05% in 15 gram tubes, NDC 0168-0140-15, 30 gram tubes, NDC 0168-0140-30, 60 gram tubes, NDC 0168-0140-60.

Store at controlled room temperature 15°-30°C (59°-86°F). Avoid temperature above 30°C (86°F).

CAUTION: Federal law prohibits dispensing without prescription.

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

R2/97
#147
I2140

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-905

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-905

3. NAME AND ADDRESS OF APPLICANT

Altana Inc.
60 Baylis Rd
Melville, NY 11747

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that, in their opinion and to the best of their knowledge all listed patents claimed in the united states for this drug product have expired, and there is no period of marketing exclusivity for the reference listed drug.

7. NONPROPRIETARY NAME

Fluocinonide

9. AMENDMENTS AND OTHER DATES:

Original 5/23/96
Amendment 8/5/96
Amendment 4/4/97
Amendment 7/14/97
Amendment 8/6/97

10. PHARMACOLOGICAL CATEGORY

Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Ointment

14. POTENCY

0.05%

15. CHEMICAL NAME AND STRUCTURE

Pregna-1,4-diene-3,20-dione,21-(acetyloxy)-6,9-difluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-,(6α,11ß,16α)

16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable

19. REVIEWER: DATE COMPLETED:

N. Nashed 8/11/97

Nashed E. Nashed, Ph.D. 8/11/97

Supervisor: Paul Schwartz, Ph.D.

8/11/97

Page(s) 9

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry Review #2.

8/11/97.

Page(s) _____

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

3/5/97

Chemistry Comments

#38

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 74-905

3. NAME AND ADDRESS OF APPLICANT

Altana Inc.
60 Baylis Rd
Melville, NY 11747

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that, in their opinion and to the best of their knowledge all listed patents claimed in the united states for this drug product have expired, and there is no period of marketing exclusivity for the reference listed drug.

7. NONPROPRIETARY NAME

Fluocinonide

9. AMENDMENTS AND OTHER DATES:

Original 5/23/96
Amendment 8/5/96

10. PHARMACOLOGICAL CATEGORY

Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM	14. POTENCY
Ointment	0.05%

15. CHEMICAL NAME AND STRUCTURE

Pregna-1,4-diene-3,20-dione,21-(acetyloxy)-6,9-difluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-,(6α,11ß,16α)

16. RECORDS AND REPORTS

17. COMMENTS

The firm will be asked to provide the reason for having overage.

The firm will be asked to provided revised certificate of analysis from their drug substance manufacturer to include limits and specifications for individual and total impurities and related substances as well their certificate of analysis to include limits and specifications for organic residual solvents

The firm will be asked to provide all available room temperature stability data.

The firm will be informed that the degradant impurities levels should be reported as percent of the active and the specifications for release of the finished drug product and stability should be revised based on their data for fluocinolone acetonide NMT f the active and others each NMT f the active and total NMT f the active.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 12/31/96

Supervisor: Paul Schwartz, Ph.D. 1/31/97

Page(s) 11

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Amnesty Review #1

1/31/97

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-905

BIOEQUIVALENCE REVIEW(S)

APPROVAL PACKAGE SUMMARY FOR 74-905

ANDA: 74-905

FIRM: Altana Inc.

DRUG: Fluocinonide

DOSAGE: Ointment

STRENGTH: 0.05%

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 10/30/96

BIO STUDY/BIOEQUIVALENCE STATUS: Bioequivalence study has been found acceptable by G.Singh 5/20/97

METHODS VALIDATION: N/A

STABILITY: The firm has submitted satisfactory accelerated stability data for three months at 40°C/75%RH and 24 months room temperature at 25-30°C/60%RH for each packaging sizes and comparative cycling study.

LABELING REVIEW STATUS: Labeling is satisfactory 4/24/97

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has provided the master formula and manufacturing instruction for the intended production batches . Also a cpoy of the executed batch record lot # 6445 was submitted. The firm will be using the same drug substance manufacture . The DMF is satisfactory 5/14/96 and same equipment and manufacture procedure.

COMMENTS: The Application is APPROVABLE.

/S/ 8/11/97

REVIEWER: Nashed E. Nashed, Ph.D. DATE: 8/11/97

SUPERVISOR: Paul Schwartz, Ph.D.

X:\NEW\FIRMSAM\ALTANA\LTRS&REV\74-905.SUM

MAY 2 9 1997

Fluocinonide
Topical Ointment, 0.05%
ANDA #74-905
Reviewer: Gur J.P. Singh.
File #74905S.596

Altana
60 Baylis Road
Melville. NY 11747
Submission Dates:
May 23. 1996. and
Feb. 26 & March 5, 1997.

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

BACKGROUND

This application contains two *in vivo* vasoconstrictor studies: a pilot dose response study and a pivotal bioequivalence study based on the June 2, 1995 guidance. This guidance was issued by the Office of Generic Drugs (OGD) for documentation of *in vivo* bioequivalence of topical dermatological corticosteroids, and it recommended the use of dose duration method to study pharmacodynamic effects of topical corticosteroids. The pharmacodynamic effect is manifested as blanching of treated skin. In this method, vasoconstrictor (skin blanching) responses of increasing durations of treatment with the test formulation are measured as a function of time after treatment administration. 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.

OGD guidance is based on recommendations of the September 12-13, 1994, Generic Drugs Advisory Committee meeting with representation of Dermatologic Drugs Advisory Committee. The committee recommended that bioequivalence of dermatologic corticosteroids be documented using the vasoconstrictor assay and the dose duration method. The dose duration to be used in the bioequivalence study comparing the test and the reference product should be based on the population ED_{50} value obtained from a 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}, 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 bioequivalence of Altana's fluocinonide 0.05% ointment is based on the above pilot-pivotal study concept. Both pilot and pivotal studies are reviewed hereafter.

PILOT DOSE RESPONSE STUDY

OBJECTIVE: To determine the population ED_{50} for the vasoconstrictor response of (I) fluocinonide 0.05% Ointment (Lidex^R 0.05% Ointment) manufactured by Hamilton Pharma and (2) desoximetasone 0.25%cream (Topicort^R 0.25% Cream). This application contains only fluocinonide ointment data.

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

Principal Investigator:

Dosing Date: 17 May , 1995

Study Protocol and Informed Consent: The protocol used for this study (#ALT 04/95F) and Informed Consent were approved by the Institutional Board.

SUBJECT SELECTION: Potential subjects were screened for vasoconstrictor response to the RLD, Lidex^R 0.05% ointment. One 5 μL application of the RLD was applied to the upper arm above the forearm and left in place for 4 hours. Skin blanching response was determined visually 2 hours after drug removal.

Fourteen healthy volunteers (9♀, 5♂) screened above were enrolled for this study, and 13 subjects (8♀, 5♂) were dosed. The mean age of these subjects was 34 ± 12 years. Subjects were selected based on acceptable medical history, negative pregnancy test and they signed informed consent. The exclusion criteria used for this study were the following:

- Significant history or current evidence of chronic or infectious skin disease.
- Strenuous exercise.
- Skin defects that may interfere with evaluation of test sites.
- Clinically significant history of alcohol or drug abuse.
- Alcohol consumption within 24 hours and throughout the study.
- Greater than 300 mg caffeine intake within 24 hours of study and during study.
- History of allergy to fluocinonide, corticosteroids, ointments, lotions, ointments or cosmetics.
- History or concurrent evidence of hypertension or other medical conditions requiring regular treatment with prescription drugs.
- Skin coloration which would interfere with assessment of skin blanching.
- Use of prescription medicine within 7 days, over-the-counter medication within 48 hours.

- Use of topical steroids on flexor surface of forearm within 30 days of dosing.
- Use of lubricant creams within 24 hours of dosing.
- Use of tobacco products within 7 days.

STUDY DESIGN: The pilot study was conducted as a single period study. Fluocinonide ointment used was Lidex^R 0.05% Ointment, lot #40427A, expiry date: 3/96.

Twelve 1 cm diameter circular skin sites were marked on both ventral forearms of each subjects. Eight sites were randomly assigned between two ventral forearms of each subject to dose durations of 15, 30, 45, 60, 90 180, 240 and 360 minutes (see pages 93, vol. 1.1). All dose durations were applied simultaneously and removed at appropriate time intervals. Thus the method of application used in this study was the *"Synchronized application and staggered removal"* method. Baseline chromameter and visual readings were recorded 1 hour prior to drug application. All designated sites were treated with approximately 5 μl aliquots of Lidex^R 0.05% Ointment. The administered formulation was dispersed over the entire spot using the conical end of a 1.5 mL polypropylene microcentrifuge tube. Skin blanching was evaluated visually as well using a chromameter from 0-27 hours after drug application. Visual scoring used the following rating scale:

SCORE	SKIN SURFACE CONDITION
0	No Pallor; no change from surrounding.
1	Minimum blanching with indistinct outline.
2	Moderate blanching with half perimeter outline.
3	Marked blanching with complete perimeter outline.
4	Maximal blanching with complete perimeter outline.

The sponsor used two brands of chromameters, i.e., 4905). Of these two chromameters, the nstruments may be better in discriminating subtle changes in skin color, based on research performed at Personnel communications). Nonetheless to be consistent with data presented in other applications on dermatologic corticosteroids, this review will focus on the data.

METHOD VALIDATION: The sponsor has documented precision of drug application and reproducibility of chromameter readings. Chromameter reproducibility was based on administration of twenty one 5 μl doses of test and reference products, on an average each skin site received 4.5 mg of the test formulation. Precision (%CV) demonstrating reproducibility of chromameter readings ranged from (pp 90, vol 1.1). Similarly %CV for ointment application ranged from

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 application using the trapezoidal rule. Similarly AUEC values were calculated based on visual scores. As noted in the pivotal study section, all chromameter AUEC values reported by the firm were not accurate. Therefore, all chromameter AUEC data used in this application is based on reviewer's calculations. The pooled AUEC data as a function of the dose duration were fitted to the simple E_{max} model using P-PHARM (Simed, France), to determine the population ED_{50}. The same analyses were also performed by the firm. Both analyses (reviewer and firm) are based on mixed effect modeling (not "naive pool" method).

RESULTS

Based on the nonlinear mixed effect modeling, values of pharmacodynamic parameters calculated by the firm and the reviewer are as follows:

Method	Parameter	Firm (A)	Reviewer (B)	A/B
Chromameter	ED_{50} (min)	75	72	1.04
	E_{max} (a scale units*min)	-46.6	-46.3	1.00
Visual Scoring	ED_{50} (min)	120	68	0.56
	E_{max} (a scale units*min)	65.1	76.9	0.84

For the analysis performed by the reviewer, the graphics illustrating the population fitting are given in appendix 1 (attachment). Based on these analyses, ED_{50} values of 72 minutes and 68 minutes were determined for the chromameter and visual data, respectively. These data are indicative of an approximate population ED_{50} value of 70 minutes, and that is the dose duration value used for the pivotal bioequivalence study.

PIVOTAL BIOEQUIVALENCE STUDY

OBJECTIVE: To determine *in vivo* bioequivalence of the test and reference fluocinonide ointments. The test product was Altana's fluocinonide 0.05% ointment and the reference product was Lidex^R 0.05% ointment manufactured by Hamilton Pharma.

STUDY SITE, PERSONNEL: Same as that mentioned for the pilot study.

Study Dates:	Group I (n=18):	December 5, 1995
	Group II (n=12):	January 3, 1996
	Group III(n=10)	January 30, 1996
	Group IV (n=12)	February 13, 1996

Study Protocol and Informed Consent: The protocol used for this study (#083195) and Informed Consent were approved by the nstitutional Review Board.

SUBJECT SELECTION: Potential subjects were screened for vasoconstrictor response to the reference listed drug Lidex^{R} 0.05% ointment as mentioned for the pilot study. All subjects were selected based on a demonstrated skin blanching response (pp 288-290).

Fifty-five healthy subjects were enrolled for this study. Of these 52 (39♀, 13♂) subjects were dosed. These subjects were 20- 57 years of age. They were enrolled based on acceptable medical history, negative pregnancy test and a signed informed consent. Criteria used for subject exclusion were the same as mentioned above for the pilot study.

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 arms as given below:

ANTECUBITAL FOSSA

Left Arm	Right Arm
D1	D2
Test	Ref
Untreated	Untreated
Ref	Test
Untreated	Untreated
Test	Ref
D2	D1
Ref	Test

WRIST

Where:

Test: Fluocinonide 0.05% ointment, Altana Pharmaceuticals, Inc., (Lot #6445, Lot size: 200 kg, manufacture date: 10/94) applied for dose duration of 70 minutes.

Ref: Lidex^R topical Ointment 0.05% (Lot #40427A, expiry date: 8/96) manufactured by Hamilton Pharma, applied for dose duration of 70 minutes.

D_1: Lidex^R topical Ointment 0.05% (Lot #40427A , expiry date: 8/96) manufactured by Hamilton Pharma Laboratories (USA), applied for dose duration of 35 minutes.

D_2: Lidex^R topical Ointment 0.05% (Lot #40427A, expiry date: 8/96) manufactured by Hamilton Pharma Laboratories (USA), applied for dose duration of 140 minutes.

TREATMENT ADMINISTRATION: Subjects were treated in four groups (n=18, 12, 10 and 12). The method of drug application and removal was consistent with that given for the pilot study. At the end of the a given treatment period, designated sites were gently wiped several times with a cotton ball. Skin blanching assessments were performed at 0, 3, 6, 9, 24, and 27 hours after drug application.

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

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.

RESULTS

Clinical Conduct of the Study: All fifty two (52) subjects dosed in this study completed the two days of evaluation. No adverse events were reported in this study.

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 correction of the chromameter raw data for the baseline and changes that occurred in the untreated skin. The corrected data were used for calculation of the pharmacodynamic metric, $AUEC_{0-24}$. Initial spot check performed by the reviewer indicated discrepancy between AUEC values calculated by the reviewer and such data submitted by the firm. Therefore the reviewer calculated all AUEC values. A comparison of the chromameter AUEC data calculated by the reviewer and the sponsor is given in table 1 (attachment), and results of reviewer's calculations do not support many AUEC values reported by the firm. Therefore, the results discussed hereafter are based on AUEC values calculated by the reviewer.

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 24 and 25 such subjects based on chromameter and visual assessment, respectively (Tables 2 and 3, attachment). For the visual assessment of skin blanching, the sponsor reported 26 evaluable subjects, instead of 25 accepted by the viewer. The observed difference is due to subject #10 whose D2/D1 ratio is 0.75, and it is lower than 1.25 recommended in the OGD guidance. 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.

With regard to the steepness of the dose response for this study, based on all 52 subjects' chromameter data, mean AUEC-D_2 was 42% greater than the mean AUEC-D_1. The difference between the pharmacodynamic responses of D_1 and D_2 based on visual scores was 23%. However, based on the "evaluable subjects" data differences between AUEC-D_2 and AUEC-D_1 were 95% and 89% using the chromameter and visual data, respectively.

Evaluation of Bioequivalence: $AUEC_{0-24}$ data for chromameter and visual assessment of skin blanching are given in tables 4 and 5 (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 UEC_{0-24} data for evaluable subjects and Locke's method are given below.

Evaluation Method	$AUEC_{0-24}$		Test/Ref	90% CI
	Test	Ref		
Chromameter	-23.49	-22.87	1.03	91-116
Visual Scoring	36.10	32.11	1.12	99-129

Based on the chromameter assessment, test product's $AUEC_{0-24}$ was 3% higher than that of the reference product. The confidence intervals comparing the test and the reference product were in the range of

Based on the visual assessment, test product's $AUEC_{0-24}$ was 12% higher than that of the reference product . The confidence intervals comparing the test and the reference product were in the range of

PRODUCT COMPOSITION (NOT TO BE RELEASED UNDER FOI):

Compositions of Altana's fluocinonide 0.05% Ointment and Lidex^R 0.05% ointment (Reference product, NDA #16909). Ingredient strengths are given as percent concentrations in finished products.

Ingredient	TEST	REF
Fluocinonide, USP	0.05%	0.05%

The sponsor indicated that the test and reference products' formulations are qualitatively identical. However, the reviewer noted that one of the inactive ingredient is labeled as in the reference product, instead of given in test product composition.

COMMENTS:

1. The sponsor performed a pilot dose response study on RLD (Lidex^R 0.05% ointment) based on the OGD guidance. Based on the nonlinear mixed effect modeling of the chromameter dose response data, an ED_{50} of approximately 72 minutes was calculated. ED_{50} value based on visual scoring was 68 minutes. For the pivotal bioequivalence study the sponsor used D_1, ED_{50} and D_2 values of 35, 70 and 140 minutes, respectively. Based on reviewer's analyses the selection of these values is appropriate.

2. Fifty two (52) subjects were dosed for pivotal bioequivalence study. All these subjects competed the study. For bioequivalence evaluation there were 24 and 25 "evaluable subjects" based on the chromameter and visual assessment of vasoconstriction, respectively.

3. Based on the chromameter evaluation of skin blanching, test product's $AUEC_{0-24}$ was 3% higher than that of the reference product. The 90% confidence intervals comparing these products were within the acceptable limit of 80-125%.

4. The sponsor also measured vasoconstriction using the visual scores method. Based on this procedure, the confidence intervals were outside the limit of 80% - 125%.

5. OGD guidance issued on June 2, 1995 recommended use of chromameter data for bioequivalence assessment (see pp 6 of the guidance). It also indicated that sponsors may rely on bioequivalence data based on visual assessment of vasoconstriction with acceptable validation (which includes establishing a correlation between the chromameter and visual data). The reviewer examined the correlation between the chromameter and visual $AUEC_{0-24}$. Using all test and reference products data (n=416), an r^2 value of 0.147 was obtained (see figure 1, attachment). When data for these products were separately analyzed. r^2 values for the test and the reference product data were 0.113 and 0.184, respectively. These data are indicative of very poor correlation between chromameter and visual assessment of skin blanching. Therefore evaluation of bioequivalence based on visual assessment of skin blanching is not warranted.

OGD guidance dose not requires documentation of bioequivalence based on both chromameter and visual assessment of vasoconstriction. Therefore evidence for bioequivalence of test and reference products based on chromameter should be considered sufficient. However, data related to visual assessment are included for completeness of this review.

6. As mentioned above all AUEC values reported by the sponsor were not correct, and the evaluation of bioequivalence is based on values calculated by the reviewer. The spreadsheets submitted in electronic formats did not contain the AUEC formula. The sponsor should be advised to correct its method of calculations of AUEC, and all future submissions should be accompanied by spreadsheets containing formulae used for all calculations.

RECOMMENDATIONS

1. The *in vivo* bioequivalence study conducted by Altana comparing its fluocinonide 0.05% ointment (lot #6445) to the reference product, Lidex^R 0.05% ointment (lot #40427A) has been found to be acceptable to the Division of Bioequivalence. The results of this vasoconstrictor study demonstrate that Altana's fluocinonide 0.05% ointment is bioequivalent to the reference product, Lidex^R 0.05% ointment, manufactured by Hamilton Pharma.

2. The sponsor should be advised of comment #6.

From the bioequivalence stand point the sponsor has met requirements of *in vivo* bioequivalence on its fluocinonide 0.05% ointment.

/S/

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

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR: /S/, 5/20/1997

CONCUR: /S/ DATE 5/29/97

Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence.

Table 3: AUEC-D1 and AUEC-D2 and their ratios based on visual scores (ANDA #74-905)

SUB	AUEC (0-24) D1	AUEC (0-24) D2	D2/D1	SUB	AUEC (0-24) D1	AUEC (0-24) D2	D2/D1
1			1.01	31			2.15
2			0.98	32			2.00
3			0.88	33			1.59
4			0.86	34			1.18
5			1.93	35			1.67
6			1.91	36			3.67
7			0.75	37			1.36
8			1.06	39			0.00
9			1.13	40			1.26
10			0.75	41			1.83
11			1.25	42			1.03
12			0.00	43			1.53
13			2.27	44			2.90
14			0.97	45			0.90
15			1.15	46			1.95
16			0.87	47			3.14
17			0.96	48			1.05
18			0.92	49			1.08
19			2.67	50			0.61
20			1.92	51			3.00
21			0.95	52			1.68
22			0.39	53			2.42
23			1.12	54			0.65
24			3.81				
25			1.10	MEAN	33.43	41.12	1.46
27			1.73	S.D	18.07	18.16	0.84
28			1.90	%CV	54	44	57
29			0.55				
30			1.48				

Table 1: Verification of chromamater AUEC values reported by the sponsor (ANDA #74-905)
Ratio values other than unity indicate inaccurate AUEC's

	TEST										REF									
Sub	Arm	Site	Hours After Drug Application					AUEC (0-24)			Arm	Site	Hours After Drug Application					AUEC (0-24)		
			0	3	6	9	24	Firm (A)	Rev (B)	A/B			0	3	6	9	24	Firm (A)	Rev (B)	A/B
1	R	1	0					-60.80	-60.80	1.00	R	2	0					-74.18	-74.18	1.00
1	R	3	0					-61.46	-61.46	1.00	R	4	0					-60.16	-60.16	1.00
1	L	2	0					-14.66	-14.66	1.00	L	1	0					-6.53	-6.53	1.00
1	L	4	0					-32.99	-32.99	1.00	L	3	0					-20.52	-20.52	1.00
2	R	2	0					-17.48	-38.81	0.45	R	1	0					-19.03	-43.78	0.43
2	R	6	0					-20.71	-42.70	0.49	R	5	0					-11.54	-20.87	0.55
2	L	1	0					-33.39	-33.39	1.00	L	2	0					-41.42	-41.42	1.00
2	L	5	0					-22.92	-22.92	1.00	L	6	0					-24.44	-24.44	1.00
3	R	2	0					-6.78	-6.78	1.00	R	1	0					-12.45	-12.45	1.00
3	R	6	0					-19.67	-19.67	1.00	R	5	0					-30.17	-30.17	1.00
3	L	1	0					0.14	0.14	0.98	L	2	0					-8.53	-8.53	1.00
3	L	5	0					-20.29	-20.29	1.00	L	6	0					-17.00	-17.00	1.00
4	R	4	0					-21.63	-21.63	1.00	R	3	0					-27.90	-27.90	1.00
4	R	6	0					-12.18	-12.18	1.00	R	5	0					-25.32	-25.32	1.00
4	L	3	0					-14.50	-14.50	1.00	L	4	0					5.75	5.75	1.00
4	L	5	0					-7.16	-7.16	1.00	L	6	0					-1.60	-1.60	1.00
5	R	3	0					-31.04	-31.04	1.00	R	4	0					-3.44	-33.44	0.10
5	R	7	0					-43.66	-43.66	1.00	R	8	0					-22.52	-22.52	1.00
5	L	4	0					-18.68	-18.68	1.00	L	3	0					-20.72	-20.72	1.00
5	L	8	0					-32.42	-32.42	1.00	L	7	0					-18.83	-18.83	1.00
6	R	6	0					-12.88	-12.88	1.00	R	5	0					-11.38	-11.38	1.00
6	R	8	0					-23.48	-23.48	1.00	R	7	0					-10.84	-10.84	1.00
6	L	5	0					5.87	5.87	1.00	L	6	0					1.67	1.67	1.00
6	L	7	0					3.87	3.87	1.00	L	8	0					-4.29	-4.29	1.00
7	R	1	0					-19.68	-19.68	1.00	R	2	0					-28.62	-28.62	1.00
7	R	3	0					-24.29	-24.29	1.00	R	4	0					-25.74	-25.74	1.00
7	L	2	0					-27.72	-27.72	1.00	L	1	0					-14.16	-14.16	1.00
7	L	4	0					-14.69	-14.69	1.00	L	3	0					-23.28	-23.28	1.00
8	R	2	0					-23.96	-23.96	1.00	R	1	0					-38.05	-38.05	1.00

8	R	6	0	-7.96	-7.96	1.00	R	7	0	-16.34	-16.34	1.00
8	L	1	0	-30.32	-30.32	1.00	L	2	0	-69.75	-69.75	1.00
8	L	7	0	-36.54	-36.54	1.00	L	8	0	-55.86	-55.86	1.00
9	R	4	0	-40.60	-40.60	1.00	R	3	0	-10.75	-10.75	1.00
9	R	6	0	-40.34	-40.34	1.00	R	5	0	-0.34	-0.34	1.01
9	L	3	0	-37.06	-37.06	1.00	L	4	0	-23.89	-23.89	1.00
9	L	5	0	-17.35	-17.35	1.00	L	6	0	-28.45	-28.45	1.00
10	R	3	0	-18.62	-18.62	1.00	R	4	0	-21.36	-21.36	1.00
10	R	7	0	-25.80	-25.80	1.00	R	8	0	-33.72	-33.72	1.00
10	L	4	0	-25.13	-25.13	1.00	L	3	0	-18.44	-18.44	1.00
10	L	8	0	-30.93	-30.93	1.00	L	7	0	-32.66	-32.66	1.00
11	R	6	0	-28.16	-28.16	1.00	R	5	0	-28.38	-28.38	1.00
11	R	8	0	-12.12	-12.12	1.00	R	7	0	-38.19	-38.19	1.00
11	L	5	0	-8.15	-8.15	1.00	L	6	0	-27.09	-27.09	1.00
11	L	7	0	-22.26	-22.26	1.00	L	8	0	-4.13	-4.13	1.00
12	R	1	0	3.43	3.43	1.00	R	2	0	-11.78	-11.78	1.00
12	R	3	0	2.59	2.59	1.00	R	4	0	-23.38	-23.38	1.00
12	L	2	0	-6.06	-6.06	1.00	L	1	0	-4.88	-4.88	1.00
12	L	4	0	-13.58	-13.58	1.00	L	3	0	-4.26	-4.26	1.00
13	R	2	0	-30.44	-30.44	1.00	R	1	0	-45.00	-45.00	1.00
13	R	6	0	-25.74	-25.74	1.00	R	5	0	-27.86	-27.86	1.00
13	L	1	0	-22.94	-22.94	1.00	L	2	0	-25.73	-25.73	1.00
13	L	5	0	-12.32	-12.32	1.00	L	6	0	-23.68	-23.68	1.00
14	R	2	0	-18.26	-18.26	1.00	R	1	0	-22.03	-22.03	1.00
14	R	6	0	-8.00	-8.00	1.00	R	5	0	-18.41	-18.41	1.00
14	L	1	0	-33.19	-33.19	1.00	L	2	0	-35.15	-35.15	1.00
14	L	5	0	-24.91	-24.91	1.00	L	6	0	-37.33	-37.33	1.00
15	R	4	0	-1.78	-1.78	1.00	R	3	0	-5.98	-5.98	1.00
15	R	6	0	-2.11	-2.11	1.00	R	5	0	-7.90	-7.90	1.00
15	L	3	0	-35.24	-35.24	1.00	L	4	0	-21.70	-21.70	1.00
15	L	5	0	-16.45	-16.45	1.00	L	6	0	-22.61	-22.61	1.00
16	R	3	0	-12.11	-12.11	1.00	R	4	0	-10.97	-10.97	1.00
16	R	7	0	-18.29	-18.29	1.00	R	8	0	-6.80	-6.80	1.00
16	L	4	0	-24.12	-24.12	1.00	L	3	0	-42.17	-42.17	1.00
16	L	8	0	-23.96	-23.96	1.00	L	7	0	-29.55	-29.55	1.00
17	R	6	0	4.36	4.36	1.00	R	5	0	-12.52	-12.52	1.00
17	R	8	0	-13.42	-13.42	1.00	R	7	0	-11.23	-11.23	1.00

17	L	5	0		-16.58	-16.58	1.00	L	6	0		-15.56	-15.56	1.00
17	L	7	0		2.01	2.01	1.00	L	8	0		-14.25	-14.25	1.00
18	R	1	0		-13.74	-13.74	1.00	R	2	0		-4.52	-4.52	1.00
18	R	3	0		1.32	1.32	1.00	R	4	0		-11.48	-11.48	1.00
18	L	2	0		-21.28	-21.28	1.00	L	1	0		-10.06	-10.06	1.00
18	L	4	0		-32.89	-32.89	1.00	L	3	0		-4.91	-4.91	1.00
19	R	1	0		-19.23	-19.23	1.00	R	2	0		-36.96	-36.96	1.00
19	R	3	0		-12.69	-12.69	1.00	R	4	0		-12.62	-12.62	1.00
19	L	2	0		-4.58	-4.58	1.00	L	1	0		1.94	1.94	1.00
19	L	4	0		-18.59	-18.59	1.00	L	3	0		-16.55	-16.55	1.00
20	R	2	0		-7.47	-14.22	0.53	R	1	0		-9.99	-18.06	0.55
20	R	6	0		-23.49	-46.98	0.50	R	5	0		-23.85	-49.44	0.48
20	L	1	0		-40.56	-40.56	1.00	L	2	0		-56.09	-56.09	1.00
20	L	5	0		-39.09	-39.09	1.00	L	6	0		-26.84	-26.84	1.00
21	R	2	0		-9.57	-9.57	1.00	R	1	0		-10.67	-10.67	1.00
21	R	6	0		-28.94	-28.94	1.00	R	5	0		-21.30	-21.30	1.00
21	L	1	0		-40.64	-40.64	1.00	L	2	0		-5.23	-5.23	1.00
21	L	5	0		-25.16	-25.16	1.00	L	6	0		-16.84	-16.84	1.00
22	R	4	0		-6.56	-6.56	1.00	R	3	0		-13.42	-13.42	1.00
22	R	6	0		-6.11	-6.11	1.00	R	5	0		-15.86	-15.86	1.00
22	L	3	0		-19.88	-19.91	1.00	L	4	0		-7.82	-7.89	0.99
22	L	5	0		-14.44	-14.54	0.99	L	6	0		0.89	0.83	1.07
23	R	3	0		-9.92	-9.92	1.00	R	4	0		-24.79	-24.79	1.00
23	R	7	0		-12.91	-12.91	1.00	R	8	0		-17.39	-17.39	1.00
23	L	4	0		-15.72	-15.72	1.00	L	3	0		-32.33	-32.33	1.00
23	L	8	0		-17.30	-17.30	1.00	L	7	0		-19.02	-19.02	1.00
24	R	6	0		-11.96	-11.96	1.00	R	5	0		1.10	1.10	1.00
24	R	8	0		-7.92	-7.92	1.00	R	7	0		4.12	4.12	1.00
24	L	5	0		-27.15	-27.15	1.00	L	6	0		-19.70	-19.70	1.00
24	L	7	0		-17.60	-17.60	1.00	L	8	0		-23.13	-23.13	1.00
25	R	1	0		-42.36	-42.36	1.00	R	2	0		-40.08	-40.08	1.00
25	R	3	0		-58.82	-58.82	1.00	R	4	0		-55.34	-55.34	1.00
25	L	2	0		-60.23	-60.23	1.00	L	1	0		-66.82	-66.82	1.00
25	L	4	0		-43.97	-43.97	1.00	L	3	0		-42.80	-42.80	1.00
27	R	4	0		-7.19	-7.19	1.00	R	3	0		-37.36	-37.36	1.00
27	R	6	0		-7.61	-7.61	1.00	R	5	0		-18.29	-18.29	1.00
27	L	3	0		-23.89	-23.89	1.00	L	4	0		-16.79	-16.79	1.00

27	L	5	0			-14.89	-14.89	1.00	L	6	0			-13.66	-13.66	1.00
28	R	3	0			-5.18	-5.18	1.00	R	4	0			-45.94	-45.94	1.00
28	R	7	0			-38.95	-38.95	1.00	R	8	0			-15.43	-15.43	1.00
28	L	4	0			-27.53	-27.53	1.00	L	3	0			-15.25	-15.25	1.00
28	L	8	0			-2.72	-2.72	1.00	L	7	0			-25.21	-25.21	1.00
29	R	6	0			-33.09	-33.09	1.00	R	5	0			-21.89	-21.89	1.00
29	R	8	0			-18.47	-18.47	1.00	R	7	0			-13.47	-13.47	1.00
29	L	5	0			-23.89	-23.89	1.00	L	6	0			-34.87	-34.87	1.00
29	L	7	0			-14.59	-14.59	1.00	L	8	0			-24.56	-24.56	1.00
30	R	1	0			-41.73	-41.78	1.00	R	2	0			-25.74	-25.76	1.00
30	R	3	0			-18.72	-18.74	1.00	R	4	0			-20.15	-20.16	1.00
30	L	2	0			-6.93	-6.87	1.01	L	1	0			-12.57	-12.63	1.00
30	L	4	0			-17.40	-17.46	1.00	L	3	0			-22.40	-22.43	1.00
31	R	2	0			-97.85	-97.85	1.00	R	1	0			-32.80	-32.80	1.00
31	R	6	0			-14.90	-14.90	1.00	R	5	0			-13.31	-13.31	1.00
31	L	1	0			-30.62	-30.62	1.00	L	2	0			-21.71	-21.71	1.00
31	L	5	0			-15.03	-15.03	1.00	L	6	0			-19.58	-19.58	1.00
32	R	1	0			-47.27	-47.27	1.00	R	2	0			-6.78	-6.78	1.00
32	R	3	0			-30.66	-30.66	1.00	R	4	0			-32.97	-32.97	1.00
32	L	2	0			-16.18	-16.18	1.00	L	1	0			-4.40	-4.40	1.00
32	L	4	0			-19.33	-19.33	1.00	L	3	0			-22.09	-22.09	1.00
33	R	2	0			-55.05	-55.05	1.00	R	1	0			-59.67	-60.23	0.99
33	R	6	0			-48.71	-48.71	1.00	R	5	0			-64.86	-64.86	1.00
33	L	1	0			-36.02	-36.02	1.00	L	2	0			-28.10	-28.10	1.00
33	L	5	0			-36.22	-36.22	1.00	L	6	0			-29.57	-29.57	1.00
34	R	2	0			-59.61	-59.61	1.00	R	1	0			-67.85	-67.85	1.00
34	R	6	0			-37.85	-37.85	1.00	R	5	0			-46.61	-46.61	1.00
34	L	1	0			-46.83	-46.83	1.00	L	2	0			-34.49	-34.49	1.00
34	L	5	0			-20.79	-20.79	1.00	L	6	0			-31.35	-31.35	1.00
35	R	4	0			-39.79	-39.79	1.00	R	3	0			-19.15	-19.15	1.00
35	R	6	0			-19.81	-19.81	1.00	R	5	0			-23.81	-23.81	1.00
35	L	3	0			-21.54	-21.54	1.00	L	4	0			-23.69	-23.69	1.00
35	L	5	0			-26.60	-26.60	1.00	L	6	0			-27.06	-27.06	1.00
36	R	3	0			-12.10	-12.10	1.00	R	4	0			10.54	10.54	1.00
36	R	7	0			-12.52	-12.52	1.00	R	8	0			1.30	1.30	1.00
36	L	4	0			-26.96	-26.96	1.00	L	3	0			-2.79	-2.79	1.00
36	L	8	0			-16.16	-16.16	1.00	L	7	0	-0.20		-6.18	-6.18	1.00

37	R	6	0		-20.98	-20.98	1.00	R	5	0		-14.24	-14.24	.00
37	R	8	0		-18.38	-18.38	1.00	R	7	0		-12.16	-12.16	1.00
37	L	5	0		-25.26	-25.26	1.00	L	6	0		-12.27	-12.27	1.00
37	L	7	0		-18.75	-18.75	1.00	L	8	0		-25.07	-25.07	1.00
39	R	2	0		-25.09	-25.09	1.00	R	1	0		-20.20	-20.20	1.00
39	R	8	0		4.03	4.03	1.00	R	7	0		-10.88	-10.88	1.00
39	L	1	0		-22.79	-22.79	1.00	L	2	0		-17.81	-17.81	1.00
39	L	7	0		-25.52	-25.52	1.00	L	8	0		-14.87	-14.87	1.00
40	R	4	0		-37.58	-37.59	1.00	R	3	0		-42.58	-12.69	3.36
40	R	6	0		-40.79	-40.80	1.00	R	5	0		-32.11	-32.19	1.00
40	L	3	0		-43.61	-43.65	1.00	L	4	0		-53.36	-53.40	1.00
40	L	5	0		-36.62	-36.66	1.00	L	6	0		-63.26	-63.30	1.00
41	R	3	0		-59.03	-59.03	1.00	R	4	0		-65.13	-65.13	1.00
41	R	7	0		-59.28	-59.28	1.00	R	8	0		-55.11	-55.11	1.00
41	L	4	0		-53.44	-53.44	1.00	L	3	0		-58.25	-58.25	1.00
41	L	8	0		-48.19	-48.19	1.00	L	7	0		-59.26	-59.26	1.00
42	R	6	0		-24.55	-24.55	1.00	R	5	0		-43.22	-43.22	1.00
42	R	8	0		-27.35	-27.35	1.00	R	7	0		-44.54	-44.54	1.00
42	L	5	0		-49.77	-49.77	1.00	L	6	0		-33.44	-33.44	1.00
42	L	7	0		-38.37	-38.37	1.00	L	8	0		-40.20	-40.20	1.00
43	R	1	0		-23.09	-23.12	1.00	R	2	0		-0.76	-0.80	0.96
43	R	3	0		-28.70	-28.76	1.00	R	4	0		10.28	10.32	1.00
43	L	2	0		-15.47	-15.50	1.00	L	1	0		-10.99	-10.98	1.00
43	L	4	0		-31.30	-31.40	1.00	L	3	0		-36.01	-36.11	1.00
44	R	2	0		-45.64	-31.17	1.46	R	1	0		-31.09	-45.09	0.69
44	R	6	0		-16.60	-21.95	0.76	R	5	0		-21.94	-16.61	1.32
44	L	1	0		-37.97	-28.35	1.34	L	2	0		-28.27	-38.06	0.74
44	L	5	0		-8.80	-26.85	0.33	L	6	0		-26.77	-8.91	3.00
45	R	2	0		7.48	7.59	0.99	R	1	0		14.03	14.12	0.99
45	R	6	0		7.16	7.25	0.99	R	5	0		-1.60	-1.61	1.00
45	L	1	0		-21.64	-21.71	1.00	L	2	0		-11.72	-11.69	1.00
45	L	5	0		-14.18	-14.25	1.00	L	6	0		-15.92	-15.89	1.00
46	R	4	0		-13.25	-13.25	1.00	R	3	0		-27.83	-27.83	1.00
46	R	6	0		-24.81	-24.84	1.00	R	5	0		-18.42	-18.42	1.00
46	L	3	0		-16.59	-16.59	1.00	L	4	0		-13.64	-13.64	1.00
46	L	5	0		-17.07	-17.07	1.00	L	6	0		-31.70	-31.70	1.00
47	R	3	0		-9.95	-10.04	0.99	R	4	0		-3.76	-3.84	0.98

47	R	7	0	2.84	2.93	0.97	R	8	0	-6.73	-6.81	0.99
47	L	4	0	6.85	6.93	0.99	L	3	0	-1.28	-1.34	0.96
47	L	8	0	10.21	10.29	0.99	L	7	0	-7.15	-7.07	1.01
48	R	6	0	-48.84	-48.86	1.00	R	5	0	-61.61	-61.62	1.00
48	R	8	0	-30.90	-30.92	1.00	R	7	0	-48.86	-48.87	1.00
48	L	5	0	-36.47	-36.56	1.00	L	6	0	-42.31	-42.39	1.00
48	L	7	0	-19.12	-19.13	1.00	L	8	0	-13.73	-13.74	1.00
49	R	1	0	-28.34	-28.37	1.00	R	2	0	-53.51	-53.57	1.00
49	R	3	0	-32.12	-32.15	1.00	R	4	0	-45.19	-45.21	1.00
49	L	2	0	-24.65	-24.68	1.00	L	1	0	-13.28	-13.31	1.00
49	L	4	0	-39.59	-39.65	1.00	L	3	0	-46.44	-46.47	1.00
50	R	2	0	9.78	9.80	1.00	R	1	0	-10.23	-10.25	1.00
50	R	8	0	-24.51	-24.53	1.00	R	7	0	-12.24	-12.23	1.00
50	L	1	0	1.69	1.58	1.07	L	2	0	14.23	-14.31	-0.99
50	R	7	0	4.66	4.61	1.01	L	8	0	-20.03	-20.15	0.99
51	R	4	0	-14.48	-14.54	1.00	R	3	0	-6.13	-6.18	0.99
51	L	6	0	-7.58	-7.64	0.99	R	5	0	-5.17	-5.19	1.00
51	L	3	0	-7.86	-7.82	1.01	L	4	0	-5.78	-5.82	0.99
51	R	5	0	-8.97	-9.02	1.00	L	6	0	-11.18	-11.22	1.00
52	R	3	0	-33.88	-33.89	1.00	R	4	0	-47.68	-47.79	1.00
52	R	7	0	-43.45	-43.56	1.00	R	8	0	-48.43	-48.54	1.00
52	L	4	0	-14.28	-14.34	1.00	L	3	0	-0.33	-0.36	0.92
52	L	8	0	-15.34	4.08	-3.76	L	7	0	-13.19	-13.22	1.00
53	R	6	0	-35.00	-35.10	1.00	R	5	0	-11.71	-11.81	0.99
53	R	8	0	-42.74	-42.84	1.00	R	7	0	-31.37	-31.44	1.00
53	L	5	0	-2.04	-2.07	0.99	L	6	0	-18.32	-18.35	1.00
53	L	7	0	3.57	3.54	1.01	L	8	0	-18.95	-19.01	1.00
54	R	1	0	-21.93	-21.95	1.00	R	2	0	5.95	5.94	1.00
54	R	3	0	-19.40	-19.41	1.00	R	4	0	-0.30	-0.32	0.95
54	L	2	0	-42.28	-42.33	1.00	L	1	0	-49.93	-49.98	1.00
54	L	4	0	-27.47	-27.53	1.00	L	3	0	-54.82	-54.87	1.00

Table 2: AUEC-D1 and AUEC-D2and their ratios based on chromameter data (ANDA #74-905)

SUB	AUEC (0-24) D1	AUEC (0-24) D2	D2/D1
1			1.08
2			1.96
3			0.97
4			1.16
5			3.50
6			-0.04
7			1.94
8			1.05
9			0.64
10			1.58
11			0.91
12			0.86
13			0.99
14			0.96
15			1.56
16			2.74
17			4.37
18			1.80
19			4.89
20			3.42
21			1.13
22			-0.23
23			1.92
24			0.86
25			1.15
27			1.59
28			3.56
29			0.96
30			3.41
31			1.75
32			1.09
33			1.60
34			1.08
35			1.26
36			3.39
37			2.19
39			1.12
40			1.21
41			1.23
42			1.35
43			1.75
44			-3.97
45			0.21
46			1.32
47			1.22
48			1.65
49			1.06
50			0.78
51			-101.23
52			0.72
53			49.77
54			-0.24
Mean	-17.22	-24.41	0.40
S.D.	13.67	15.34	15.91
%CV	79	63	-3941

Table 4A: Test and Reference product's values based on reviewer's calculations (ANDA #74-905, Chromameter data)

Sub	AUEC (0-24) TEST	AUEC (0-24) REF
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
27		
28		
29		
30		
31		
32		
33		
34		
35		
36		
37		
39		
40		
41		
42		
43		
44		
45		
46		
47		
48		
49		
50		
51		
52		
53		
54	-27.80	
Mean	-22.96	-23.33
S.D	12.45	13.34
%CV	54	57

Table 4B: Test and Reference product's values used for calculation of 90% confidence intervals (ANDA #74-905, Chromameter data)

Sub	AUEC (0-24) TEST	REF
2		
5		
7		
10		
15		
16		
17		
18		
19		
20		
23		
27		
28		
30		
31		
33		
35		
36		
37		
42		
43		
46		
48		
53		
Mean	-23.49	-22.87
S.D	9.65	10.94
%CV	41	48

Table 5A: Test and Reference product's values based on visual score data (ANDA #74-905)

Sub	AUEC (0-24) TEST	AUEC (0-24) REF
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
27		
28		
29		
30		
31	4	5
32	4	3
33	1	0
34	5	3
35	1	5
36	2	3
37	2	5
39	2	5
40	5	0
41	5	3
42	5	3
43	5	0
44	2	3
45	5	5
46	4	3
47	1	0
48	2	0
49	6	5
50		3
51		3
52	4	0
53	4	3
54	5	5
mean	38.30	36.66
SD	16.36	17.55
CV%	43	48

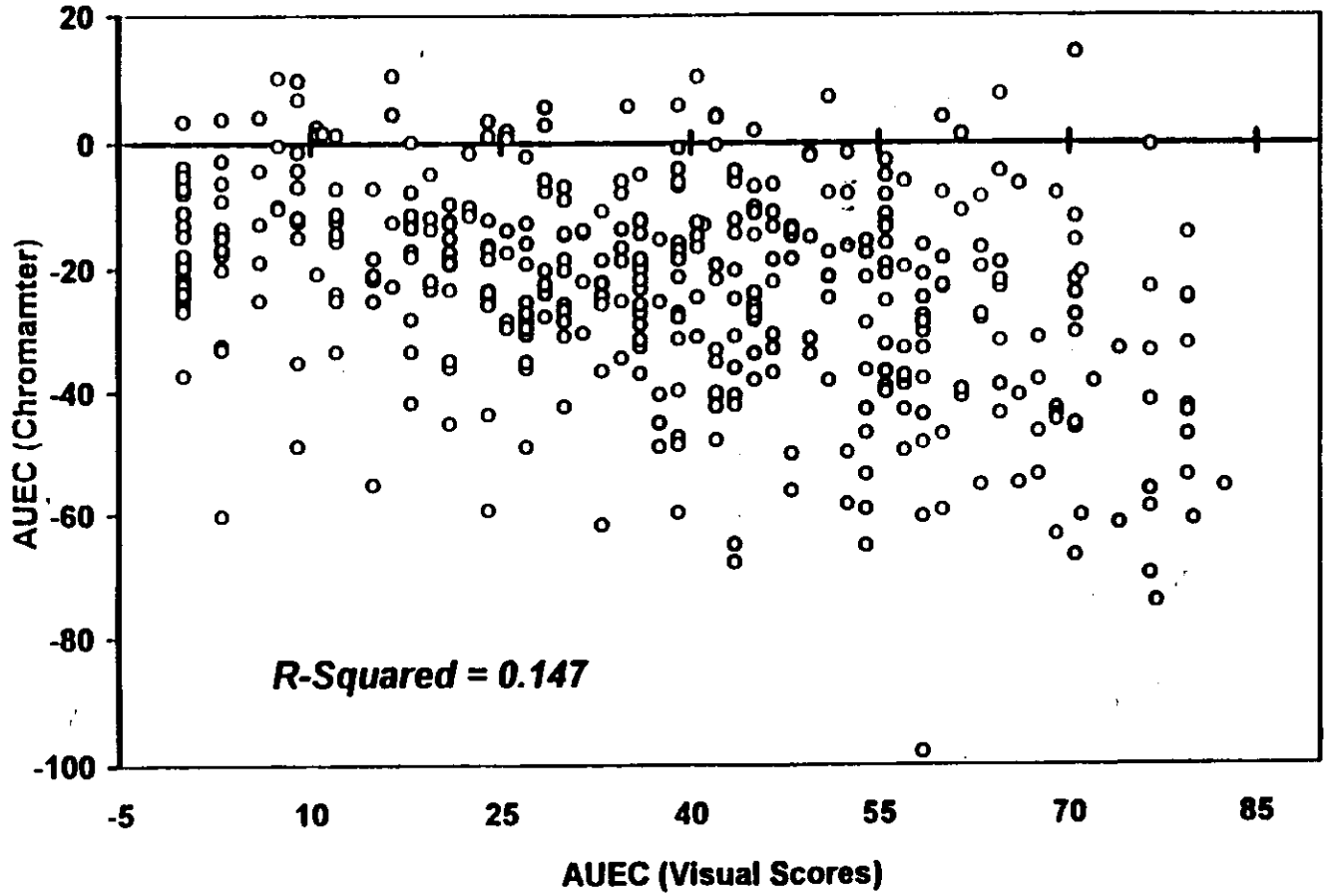
Highlighted cells indicate test and reference products' data used for bioequivalence comparisons

Table 5B: Test and Reference product's values used for calculation of 90% confidence intervals (ANDA #74-905)

	AUEC (0-24)	
Sub	TEST	REF
5		
6		
11		
13		
19		
20		
24		
27		
28		
30		
31		
32		
33		
35		
36		
37		
40		
41		
43		
44		
46		
47		
51		
52		
53		
mean	38.10	32.11
SD	15.27	16.42
CV%	42	51

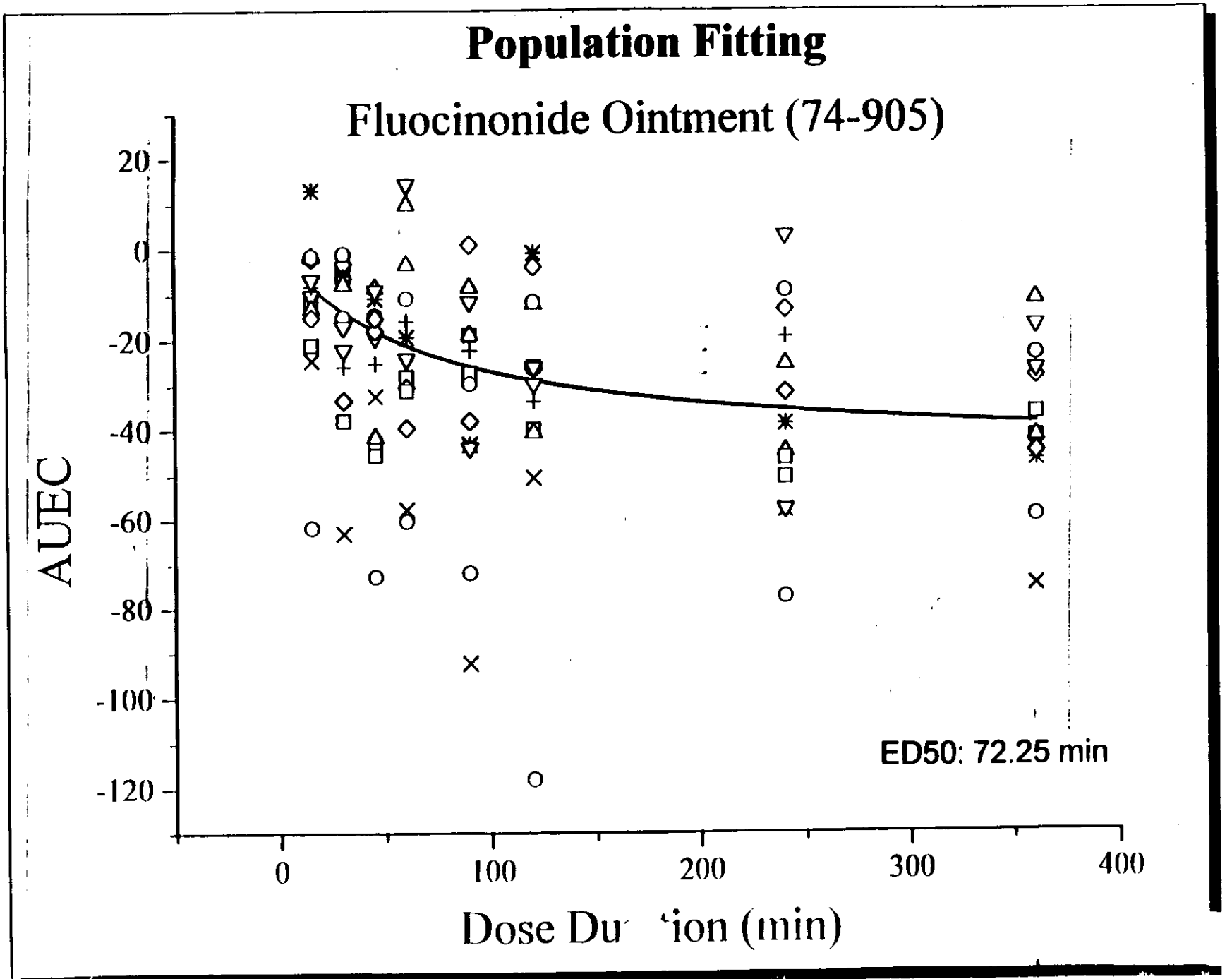
Note: The sponsor included subjects #10 for confidence interval calculations. The reviewer has excluded that subject because its D2/D1 ratio is 0.75. The sponsor has reported the same D2/D1 ratio for this subject (pp 747, vol. 1.2)

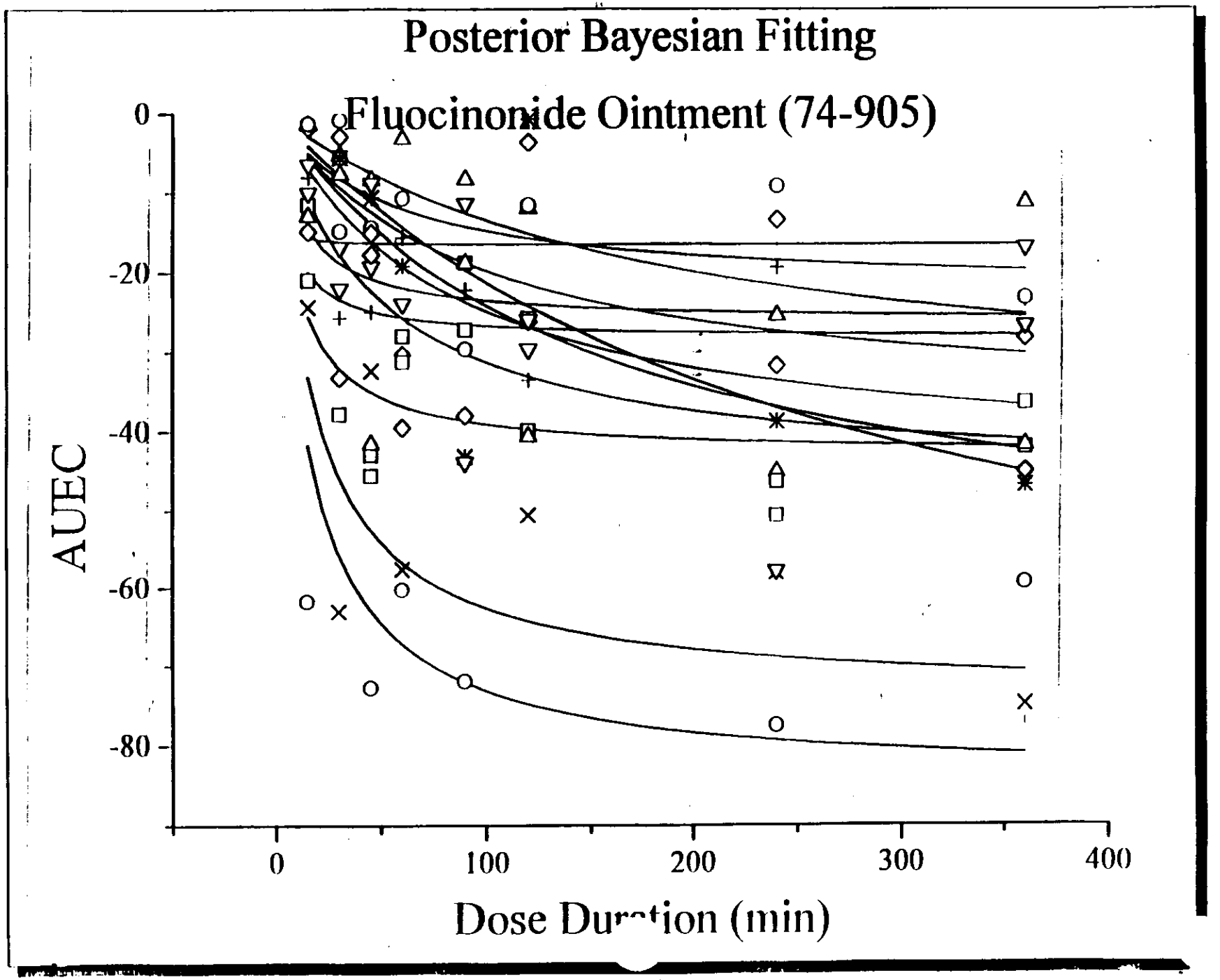
Figure 1. Correlation between AUEC (0-24) values based on chromameter data and visual scores (ANDA #74-905)

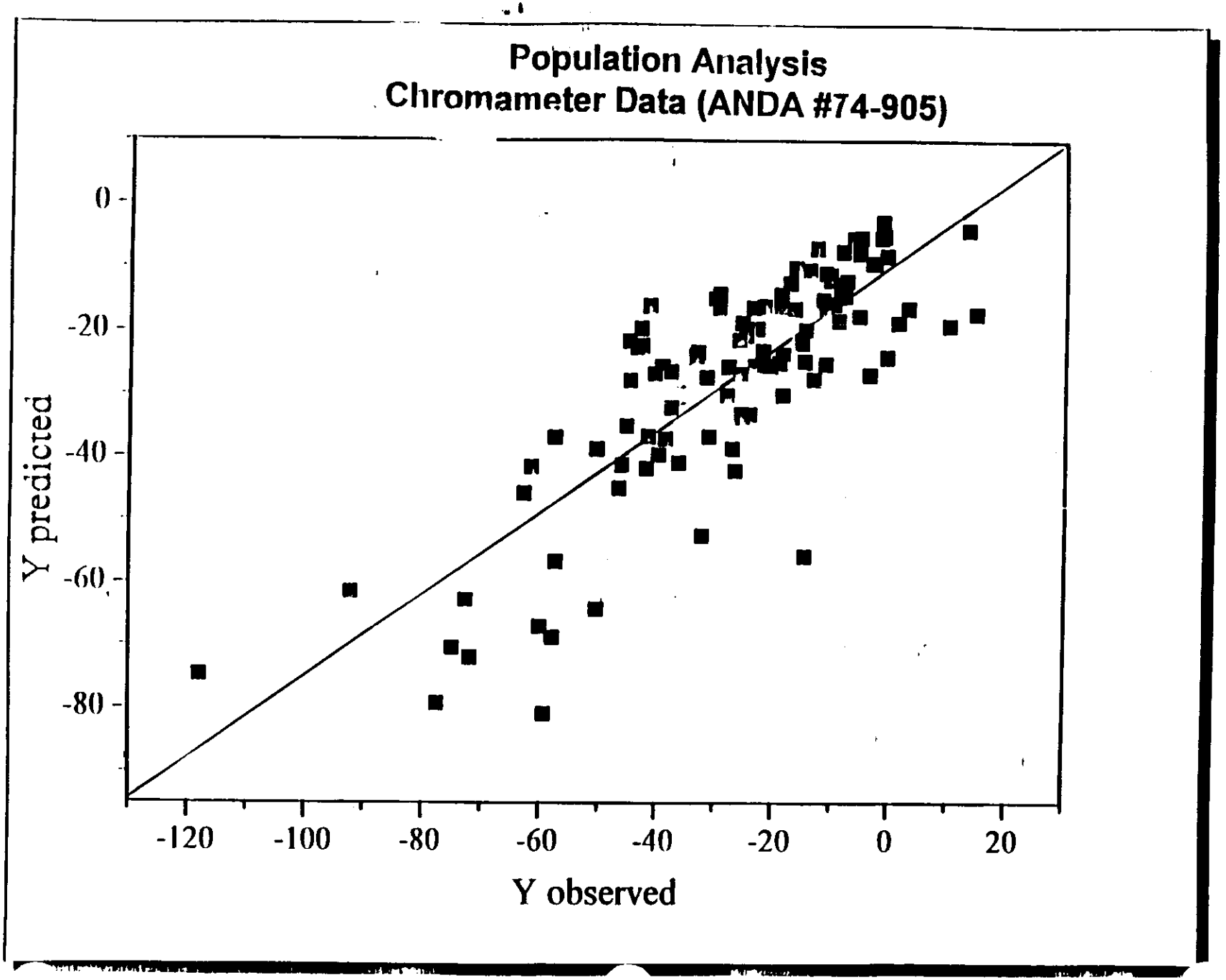


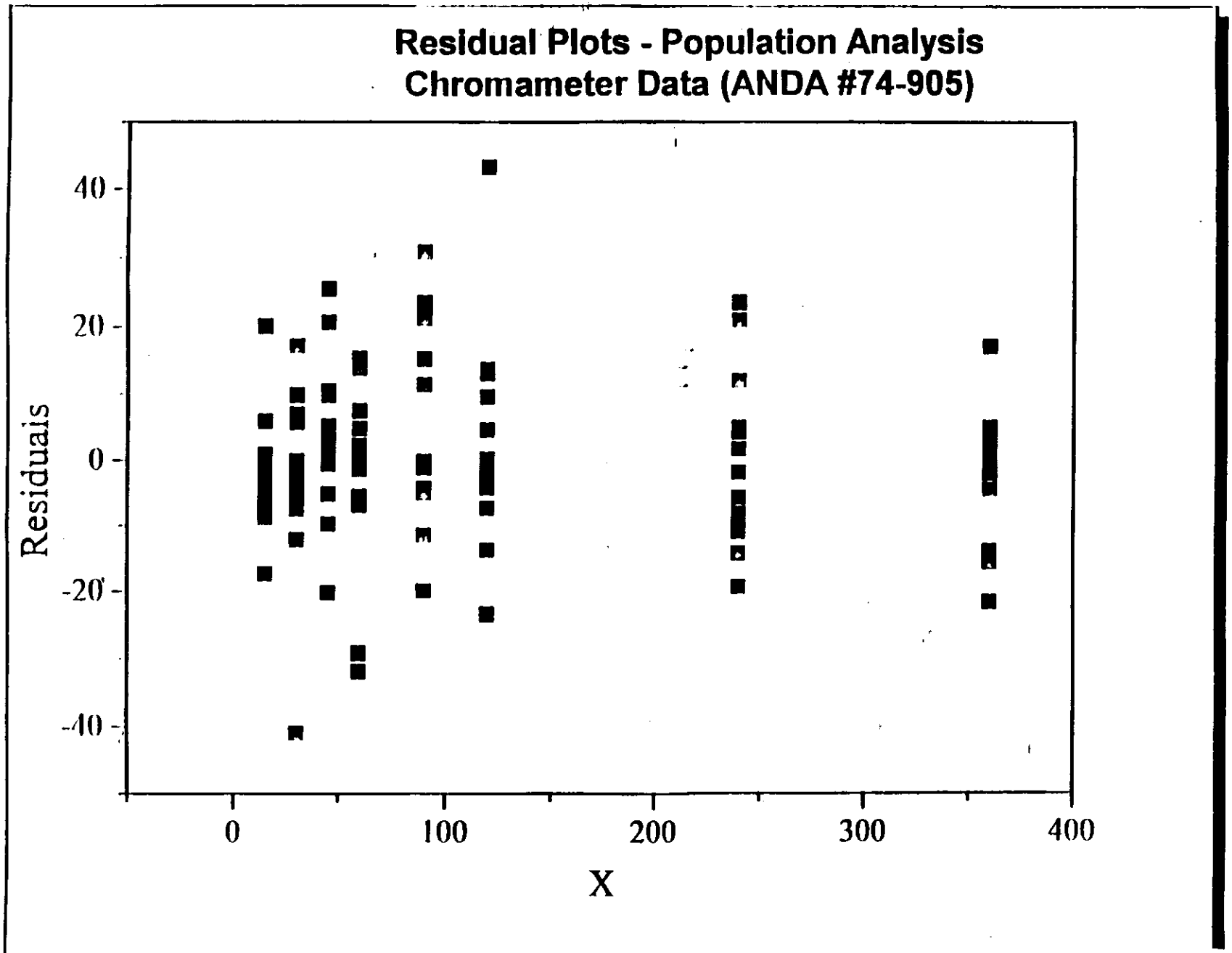
APPENDIX 1

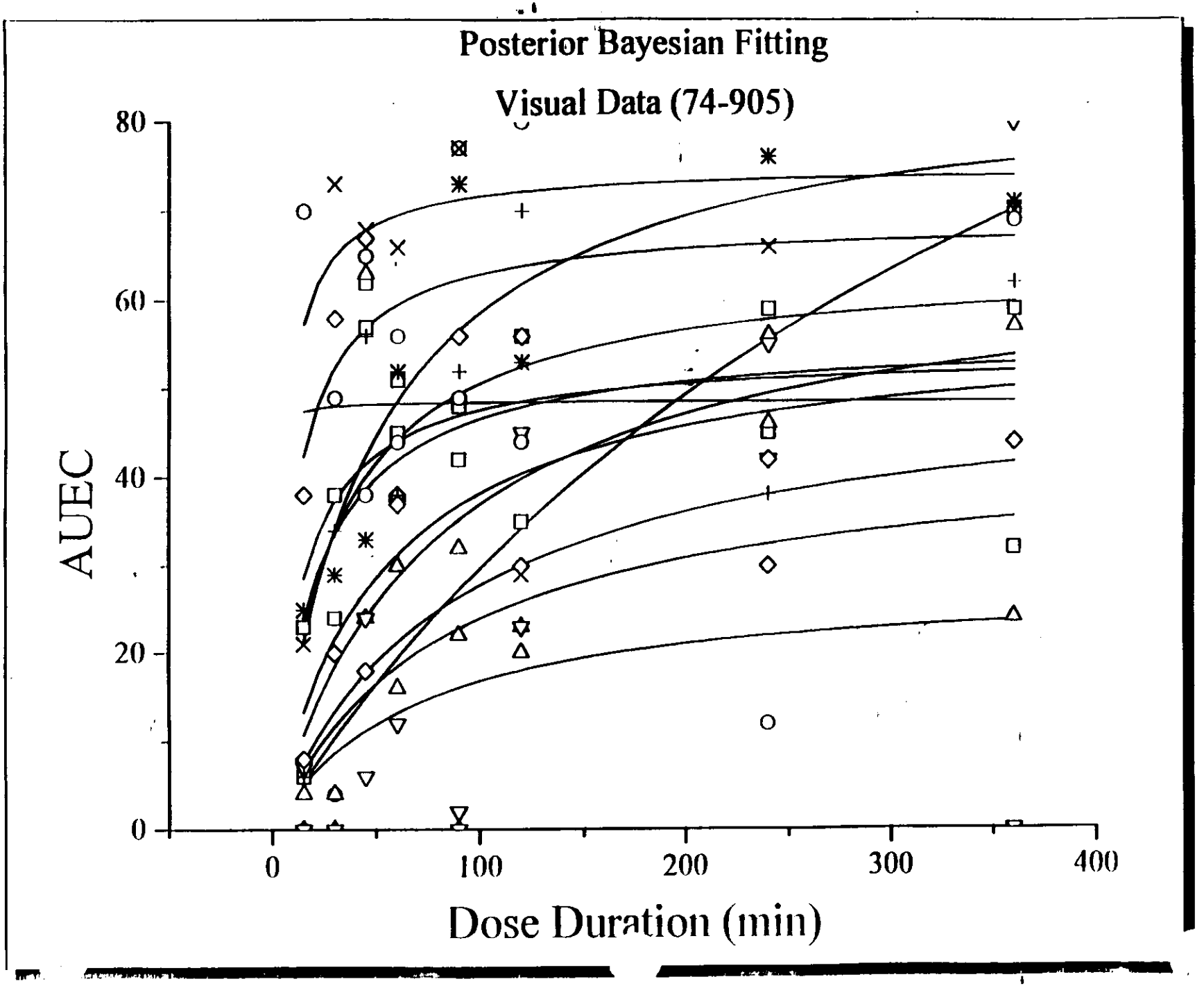
Nonlinear Mixed Effect Modeling of the Pilot Study Data

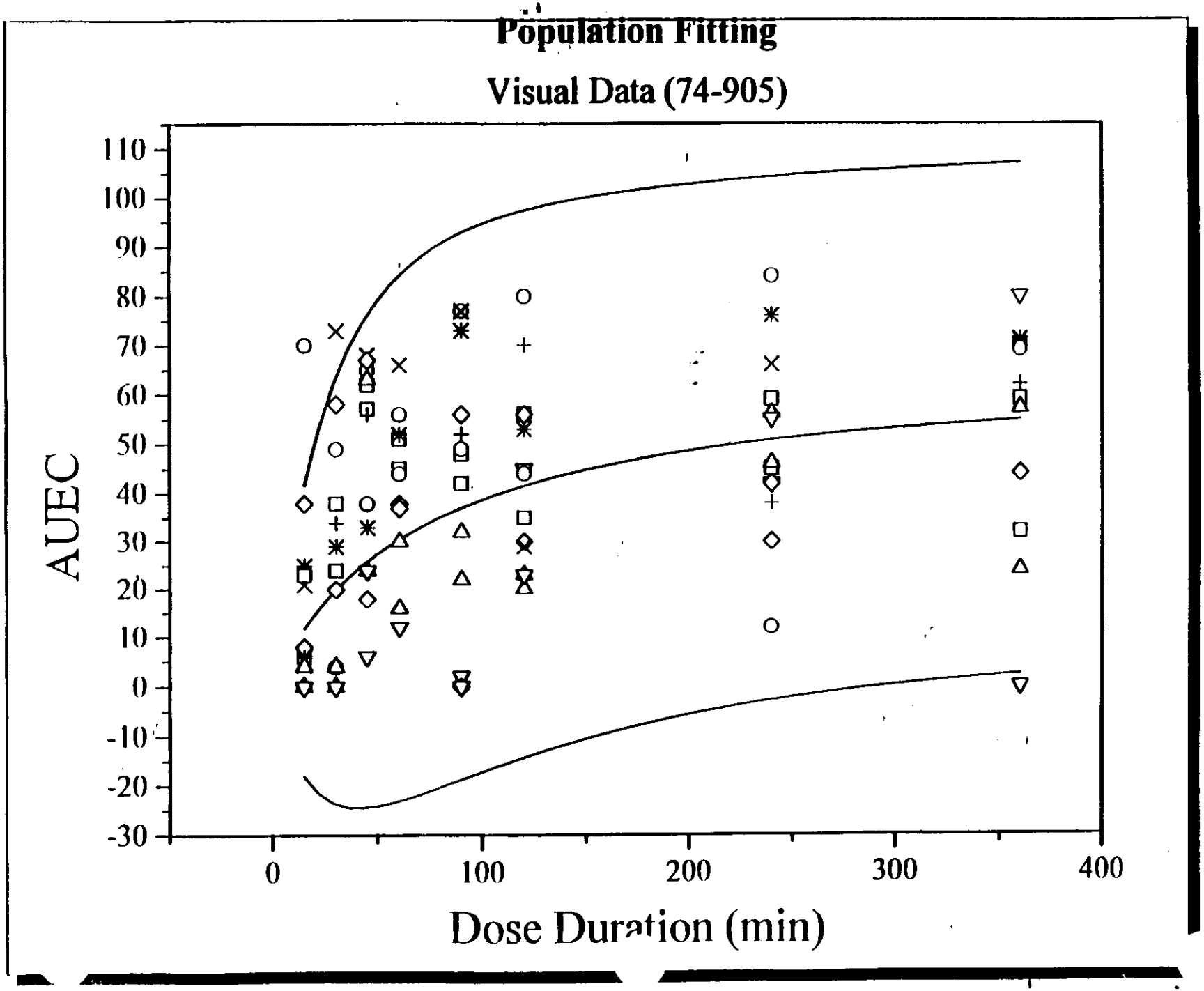

Population Fitting
Fluocinonide Ointment (74-905)
AUEC
20
0
-20
-40
-60
-80
-100
-120
0
100
200
300
400
Dose Du 'ion (min)
ED50: 72.25 min

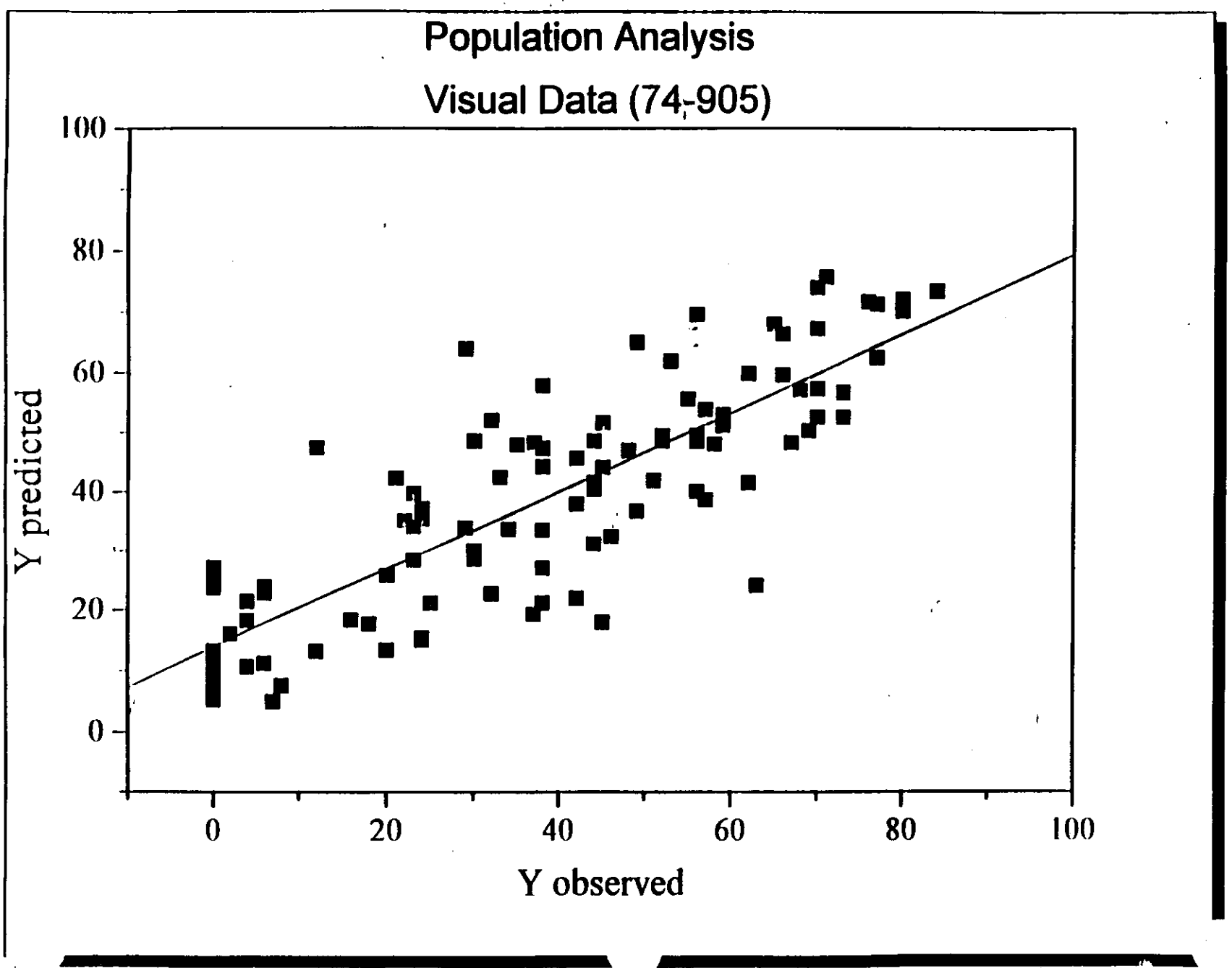

Posterior Bayesian Fitting
Fluocinonide Ointment (74-905)
AUEC
0
-20
-40
-60
-80
0
100
200
300
400
Dose Duration (min)

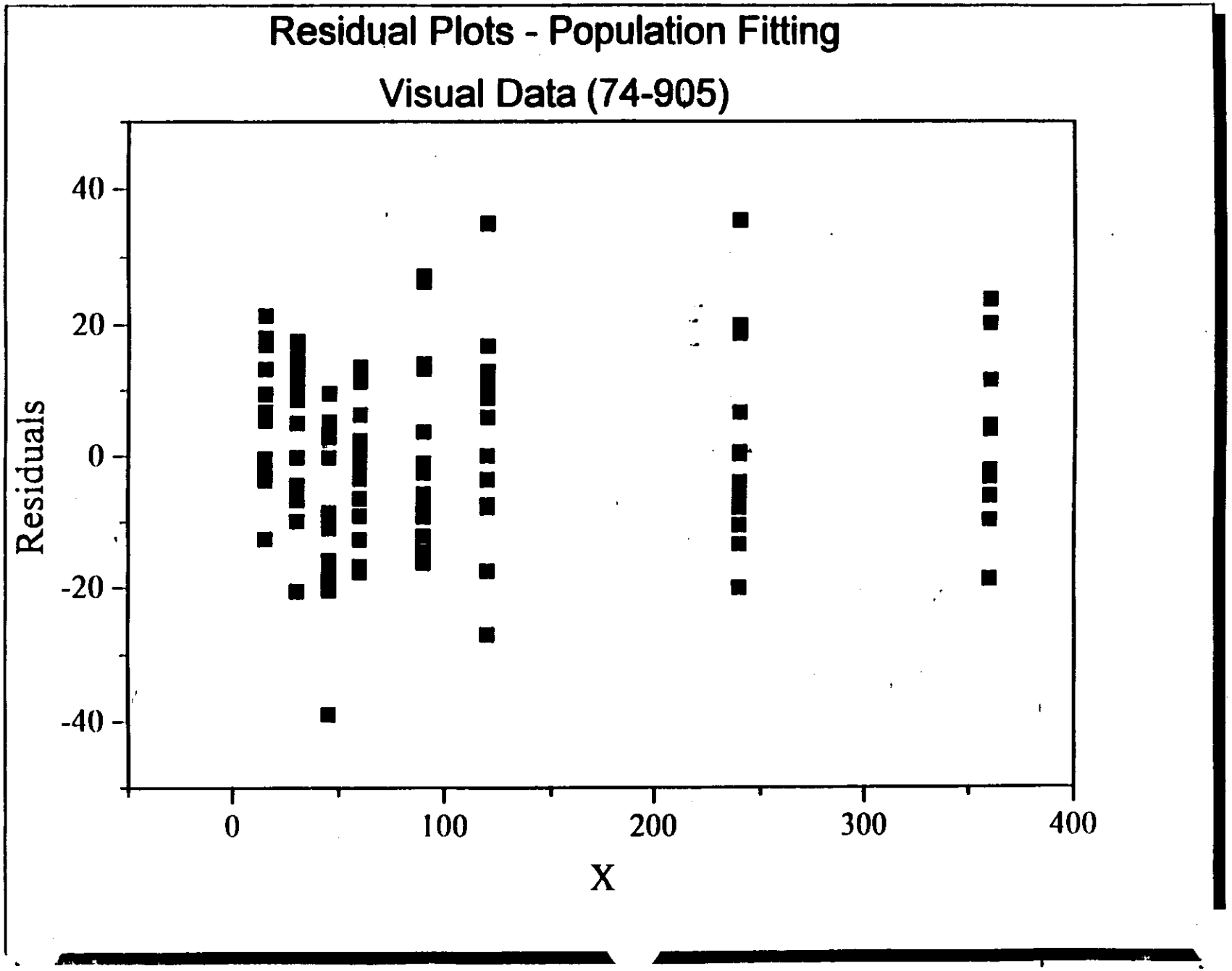

Population Analysis
Chromameter Data (ANDA #74-905)
Y predicted
0
-20
-40
-60
-80
-120
-100
-80
-60
-40
-20
0
20
Y observed


Residual Plots - Population Analysis
Chromameter Data (ANDA #74-905)
Residuals
40
20
0
-20
-40
0
100
200
300
400
X


Posterior Bayesian Fitting
Visual Data (74-905)
AUEC
80
60
40
20
0
0
100
200
300
400
Dose Duration (min)


Population Fitting
Visual Data (74-905)
AUEC
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
0
100
200
300
400
Dose Duration (min)


Population Analysis
Visual Data (74-905)
Y predicted
Y observed
0
20
40
60
80
100


Residual Plots - Population Fitting
Visual Data (74-905)
Residuals
40
20
0
-20
-40
0
100
200
300
400
X

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-905

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION/MEETING

Reference is made to Altana's fax dated 7/14/97 (attached).

After review of the data, OGD provided the following comments to the firm.

1. OGD sees no trend in inhomogeneity in the RLD.

2. OGD recommends an additional test comparing the generic to the RLD under the following cycling conditions:

2 days at 4 degrees C
2 days at 40 degrees C

2 days at 4 degrees C
2 days at 40 degrees C

2 days at 4 degrees C
2 days at 40 degrees C

Total: 3 cycles and 12 days

The firm agrees to provide the data and discuss in 2 weeks.

x:\new\firmsam\altana\telecons\74905.001

cc:
ANDA
Div File
T-con Binder

DATE
7/15/97

ANDA NUMBER
74905

IND NUMBER

TELECON

INITIATED BY FDA
Allen Rudman
Paul Schwartz
Nashed Nashed
Joe Buccine

PRODUCT NAME
Fluocinonide Ointment 0.05%

FIRM NAME
Altana

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Virginia Carman
Dave Pierce

TELEPHONE NUMBER
(516) 454-7677

SIGNATURE

/S/
Joseph Buccine

CDER Establishment Evaluation Report
for March 21, 1997

Application: ANDA 74905/009
Stamp: 24-MAY-1996 Regulatory Due:
Applicant: ALTANA
60 BAYLIS RD
MELVILLE, NY 11747

Priority:
Action Goal:
Brand Name:
Established Name: FLUOCINONIDE
Generic Name:
Dosage Form: ONT (OINTMENT)
Strength: 0.05%

Org Code: 600
District Goal: 24-JUL-1997

FDA Contacts:

Overall Recommendation:

ACCEPTABLE on 30-OCT-1996 by M. EGAS (HFD-324) 301-827-0062

Establishment: 2410271
ALTANA INC
CANTIAGUE ROCK RD
HICKSVILLE, NY 11802

DMF No:

Profile: OIN OAI Status: NONE
Last Milestone: OC RECOMMENDATI 30-OCT-1996
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Establishment: 2432435
ALTANA INC
60 BAYLIS RD
MELVILLE, NY 11747

DMF No:

Profile: NEC OAI Status: NONE
Last Milestone: OC RECOMMENDATI 30-OCT-1996
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:
FINISHED DOSAGE OTHER TESTER

Establishment

:C OAI Status: NONE
ne: OC RECOMMENDATI 30-OCT-1996
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:
FINISHED DOSAGE OTHER TESTER

Establishment:

SN OAI Status: NONE
one: OC RECOMMENDATI 30-OCT-1996
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA#: 74-905 **SPONSOR:** Altana
DOSAGE FORM: Fluocinonide ointment
STRENGTHS(s): 0.05%
TYPE OF STUDY: Pilot dose- response and pivotal bioequivalence studies.
STUDY SITE: University of Utah Health Science Center, Salt Lake City, Utah.

STUDY SUMMARY: The sponsor submitted a plot dose-response study and a pivotal bioequivalence study based on June 2, 1995, OGD guidance. The pilot study was conducted to determine population ED_{50} for the reference product, Lidex^R 0.05% ointment (Hamilton Pharma). Based on this study an ED_{50} of 72 minutes was determined.

In the pivotal bioequivalence study, test and reference products were compared at a dose duration of 70 minutes. Comparison of these products was based on the Area Under the Effect Curve (AUEC) using chromameter and visual assessments of vasoconstriction. Based on the chromameter data, 90% confidence intervals for the AUEC were within the acceptable range of 80-125%. However, AUEC-90% confidence intervals based on visual scores data were not within the acceptable range of 80-125%. The assessment of bioequivalence is based solely on chromameter data because there was no correlation between AUEC data based on the chromameter and visual assessments of skin blanching. The results of the pivotal bioequivalence study demonstrate that Altana's fluocinonide 0.05% ointment is bioequivalent to the reference product, Lidex^R 0.05% ointment, manufactured by Hamilton Pharma.

***IN VITRO* RELEASE DATA:** The sponsor did not submit comparative *in vitro* release data. Based on the June 2, 1995, OGD guidance, *in vitro* release data are not required to support *in vivo* bioequivalence of the test product.

PRIMARY REVIEWER: Gur J.P. Singh, Ph.D. **BRANCH:** II

INITIAL /S/ DATE 5-5-97

TEAM LEADER: Shriniwas Nerurkar, Ph.D. **BRANCH:** II

INITIAL: /S/ DATE 5/20/97

for **DIRECTOR, DIVISION OF BIOEQUIVALENCE:** Nicholas Fleischer, Ph.D.

INITIAL: /S/ DATE 5/29/97

DIRECTOR, OFFICE OF GENERIC DRUGS

INITIAL: _____ DATE _____

Application: **ANDA 74905/000**
Stamp: **24-MAY-1996** Regulatory Due:
Applicant: **ALTANA**
60 BAYLIS RD
MELVILLE, NY 11747

Priority:
Action Goal:
Brand Name:
Established Name: **FLUOCINONIDE**
Generic Name:
Dosage Form: **ONT (OINTMENT)**
Strength: **0.05%**

Org Code: **600**
District Goal: **24-JUL-1997**

FDA Contacts:

Overall Recommendation:

ACCEPTABLE on 30-OCT-1996 by M. EGAS (HFD-322) 301-594-0095

Establishment: **2410271**
ALTANA INC
CANTIAGUE ROCK RD
HICKSVILLE, NY 11802

DMF No:

AADA No:

Profile: **OIN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 30-OCT-1996**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Establishment: **2432435**
ALTANA INC
60 BAYLIS RD
MELVILLE, NY 11747

DMF No:

AADA No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 30-OCT-1996**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
FINISHED DOSAGE OTHER TESTER

Establishment:

MF No:

AADA No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 30-OCT-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:
FINISHED DOSAGE OTHER TESTER

Establishment:

DMF No:

AADA No:

Responsibilities:

DRUG SUBSTANCE MANUFACTURER

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 30-OCT-1996**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-905 Date of Submission: April 4, 1997

Applicant's Name: Altana Inc.

Established Name: Fluocinonide Ointment USP, 0.05%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (15 g, 30 g, and 60 g tubes)
Satisfactory as of April 4, 1997 submission.

Carton Labeling: (15 g, 30 g, and 60 g tubes)
Satisfactory as of April 4, 1997 submission.

Professional Package Insert Labeling:
Satisfactory as of April 4, 1997 submission.

Revisions needed post-approval:

PACKAGE INSERT LABELING

1. DESCRIPTION

   Revise the molecular weight to read, 494.54.

2. DOSAGE AND ADMINISTRATION

   Revise the first sentence to read, ...two to four...

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Lidex® Ointment

NDA Number: 16-909

NDA Drug Name: Fluocinonide Ointment USP, 0.05%

NDA Firm: Hamilton Pharma, Inc.

Date of Approval of NDA Insert and supplement #043: March 12, 1991

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: 16-909

Basis of Approval for the Carton Labeling: 16-909

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	

Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			

Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FYR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. Labeling review was based on the reference listed drug (Lidex Ointment, 0.05% - Hamilton Pharma, Inc.; revised January 1990; approved March 12, 1991). ANDA 73-481 (Lemmon's approved ANDA for the ointment) was also used as guidance for the storage recommendations.

   The recommendation on the approved labeling is inconsistent between the container/carton and insert. The insert reads "Store at room temperature. Avoid temperature above 30°C (86°F)"; the carton and container labeling approved 1981 read, "Avoid excessive heat over 40°C (104°F); however, new labeling reflects the 30° limit. We approved the 1981 recommendation in ANDA 73-481. The side-by-side submitted by Altana used the 30° temp. So, in considering the effect a slight temperature rise has on ointment, it was decided to use the CRT/30° limit recommendation. This also reinforces the CRT upper limit.

2. Packaging
   Altana proposes to package its product in 15 g, 30 g, and 60 g white aluminum tubes. The RLD packages its product in 15 g, 30 g, 60 g, and 120 g containers.

3. The inactive ingredients listed in the DESCRIPTION section of the package insert agree with those listed in the C&C statement found in volume 1.4, section VII.

4. ~~USP Issues~~ Storage
   USP - Preserve in collapsible tubes or tight containers.

   RLD - Store at room temperature. Avoid temperature above 30°C (86°F)

   ANDA - Inconsistent recommendations. Will be asked to revise to read, "Store at CRT 15-30°C (59-86°F). Avoid ~~temperatures above 30°C (86°F).~~

5. Bio issues are pending.

6. There are no Patent or exclusivity issues pending.

not needed unless extension over 30° heat detrimental effect on ointment

Date of Review:
April 24, 1997

Date of Submission:
April 4, 1997

Primary Reviewer: /S/ Date: 4/21/97

Secondary Reviewer: /S/ Date: 4/24/97

Team Leader: /S/ Date: 4/24/97

cc:

RECORD OF TELEPHONE CONVERSATION/MEETING

Virginia Carman was contacted to request a diskette with all data for pilot and pivotal studies. The diskettes should be in Excell format P.C. (Not in MacIntosh).

2/28/97
Diskette containing information described above received. However, it is not complete. Raw and corrected data for chromameter and visual assessment is missing. Please submit in P.C. Excell formatted spread sheets.

DATE
2/24/97

AADA NUMBER
74905

IND NUMBER

TELECON

INITIATED BY **MADE**
_ **APPLICANT/SPONSOR** _ **BY TELE.**
X **FDA** _ **IN PERSON**

PRODUCT NAME
Fluocinonide Ointment 0.05%

FIRM NAME
Altana

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Virginia Carman, Associate Director, Reg. Affairs

TELEPHONE NUMBER
(516) 454-7677

SIGNATURE
L. Sanchez, Pharm.D.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-905 Date of Submission: May 23, 1996

Applicant's Name: Altana Inc.

Established Name: Fluocinonide Ointment USP, 0.05%

Labeling Deficiencies:

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

   a. Revise storage recommendation to include, "Avoid temperature above 30°C (86°F)".

   b. Revise the "Each gram contains" statement to read, "Fluocinonide 0.5 mg solubilized...". (Delete "/g").

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

   a. See CONTAINER comments.

   b. Revise "Each mL contains" to read, "Each gram contains".

3. INSERT

   a. DESCRIPTION

      i. Revise the chemical name to read, "...9-difluoro..."

      ii. Revise to include the molecular weight and molecular formula.

      iii. Revise the second paragraph to read, "Each gram of Fluocinonide..."

      iv. Revise the last sentence of the first paragraph to read, "...following structural formula:"

   b. INDICATIONS AND USAGE

      Revise to read, "...corticosteroid-responsive...".

c. PRECAUTIONS

i. GENERAL COMMENT

Please revise subsection headings to be consistent in format (e.g., italicized)

ii. General

Revise the first sentence of paragraph 3 to read, "Therefore, patients receiving a large...".

iii. Information for the patient

A) Make the following the first sentence of this subsection:

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

B) Delete the extra space between instruction 3 and 4.

C) Revise instruction 5 to read, "...diapers or plastic...".

iv. Carcinogenesis, Mutagenesis, and Impairment of Fertility

A) Revise to delete "and" in the subsection heading.

B) Revise the first sentence to read, "Long-term...".

C) Revise to let sentence 2 begin a new paragraph.

v. Pregnancy Category C

A) Revise the subsection heading to read:

Pregnancy. Teratogenic Effects. Pregnancy Category C

B) Revise the penultimate sentence to read, "...potential benefit...".

C) Revise the ultimate sentence to read, "...patients, in large...".

vi. Pediatric Patients

Revise the penultimate sentence to read, "...to the least amount...".

d. DOSAGE AND ADMINISTRATION

Revise the ultimate sentence to read, "If an infection...".

e. HOW SUPPLIED

Revise the storage recommendations to read, "Store at controlled room temperature 15° - 30°C (59° - 86°F). Avoid temperature above 30°C (86°F).

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE *(Check One)* ☒ Original ☐ FollowUp ☐ FUR	DATE August 16, 1996	PHONE NO. (301)594-1841	[redacted]
REQUESTORS NAME: William Russell	DIVISION: Office of Generic Drugs		MAIL CODE: HFD-629
APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-905			
BRAND NAME:	ESTABLISHED NAME: Fluocinonide Ointment		
DOSAGE STRENGTH: 0.05%			STERILE ☐Yes ☒ No
PROFILE CLASS:: OIN	PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)*		
APPLICANT'S NAME: Altana, Inc.			
APPLICANT'S ADDRESS: 60 Baylis Road Melville, NY 11747			
COMMENTS :			

FACILITIES TO BE EVALUATED
(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID
1. Applicant	Testing facility		[redacted]
		nec	
	Manufacturing facility		
		oin	
3.	Manufacturer o NDS		
		csn	
4.	Testing facility		
		nec	
5.			

[redacted]

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE *(Check One)* ☒ Original ☐ FollowUp ☐ FUR	DATE August 16, 1996	PHONE NO. (301)594-1841
REQUESTORS NAME: William Russell	DIVISION: Office of Generic Drugs	MAIL CODE: HFD-629
APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-905		
BRAND NAME:	ESTABLISHED NAME: Fluocinonide Ointment	
DOSAGE STRENGTH: 0.05%		STERILE ☐Yes ☒ No
PROFILE CLASS:: OIN	PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)*	
APPLICANT'S NAME: Altana, Inc.		
APPLICANT'S ADDRESS: 60 Baylis Road Melville, NY 11747		
COMMENTS :		

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID
1. Applicant	Testing facility	nec	
2.	Manufacturing facility	oin	
3	Manufacturer of NDS	csn	
4	Testing facility	nec	
5.			

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.

cc
x:\

1.1
Schwartz, P.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-905 Date of Submission: May 23, 1996

Applicant's Name: Altana Inc. 8/5/96 per J. Carver

Established Name: Fluocinonide Ointment USP, 0.05%

Labeling Deficiencies:

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

   a. Revise storage recommendation to include, "Avoid temperature above 30°C (86°F)".

   b. Revise the "Each gram contains" statement to read, "Fluocinonide 0.5 mg solubilized...". (Delete "/g").

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

   a. See CONTAINER comments.

   b. Revise "Each mL contains" to read, "Each gram contains".

3. INSERT

   a. DESCRIPTION

      i. Revise the chemical name to read, "...9-difluoro..."

      ii. Revise to include the molecular weight and molecular formula.

      iii. Revise the second paragraph to read, "Each gram of Fluocinonide..."

      iv. Revise the last sentence of the first paragraph to read, "...following structural formula:"

   b. INDICATIONS AND USAGE

      Revise to read, "...corticosteroid-responsive...".

c. PRECAUTIONS

i. GENERAL COMMENT

Please revise subsection headings to be consistent in format (e.g., italicized)

ii. General

Revise the first sentence of paragraph 3 to read, "Therefore, patients receiving a large...".

iii. Information for the patient

A) Make the following the first sentence of this subsection:

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

B) Delete the extra space between instruction 3 and 4.

C) Revise instruction 5 to read, "...diapers or plastic...".

iv. Carcinogenesis, Mutagenesis, and Impairment of Fertility

A) Revise to delete "and" in the subsection heading.

B) Revise the first sentence to read, "Long-term...".

C) Revise to let sentence 2 begin a new paragraph.

v. Pregnancy Category C

A) Revise the subsection heading to read:

Pregnancy. Teratogenic Effects. Pregnancy Category C

B) Revise the penultimate sentence to read, "...potential benefit...".

C) Revise the ultimate sentence to read, "...patients, in large...".

vi. Pediatric Patients

Revise the penultimate sentence to read, "...to the least amount...".

d. DOSAGE AND ADMINISTRATION

Revise the ultimate sentence to read, "If an infection...".

e. HOW SUPPLIED

Revise the storage recommendations to read, "Store at controlled room temperature 15° - 30°C (59° - 86°F). Avoid temperature above 30°C (86°F).

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/s/ Jerry Phillips

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name			
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration; never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling (continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FPR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FPR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FPR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FPR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. **Labeling review was based on the reference listed drug (Lidex Ointment, 0.05% - Hamilton Pharma, Inc.; revised January 1990; approved March 12, 1991). ANDA 73-481 (Lemmon's approved ANDA for the ointment) was also used as guidance for the storage recommendations.**

   The recommendation on the approved labeling is inconsistent between the container/carton and insert. The insert reads "Store at room temperature. Avoid temperature above 30°C (86°F)"; the carton and container labeling approved 1981 read, "Avoid excessive heat over 40°C (104°F); however, new

labeling reflects the 30° limit. We approved the 1981 recommendation in ANDA 73-481. The side-by-side submitted by Altana used the 30° temp. So, in considering the effect a slight temperature rise has on ointment, it was decided to use the CRT/30° limit recommendation. This also reinforces the CRT upper limit.

2. Packaging
Altana proposes to package its product in 15 g, 30 g, and 60 g white aluminum tubes. The RLD packages its product in 15 g, 30 g, 60 g, and 120 g containers.

3. The inactive ingredients listed in the DESCRIPTION section of the package insert agree with those listed in the C&C statement found in volume 1.4, section VII.

4. USP Issues
USP - Preserve in collapsible tubes or tight containers.

RLD - Store at room temperature. Avoid temperature above 30°C (86°F)

ANDA - Inconsistent recommendations. Will be asked to revise to read, "Store at CRT 15-30°C (59-86°F). Avoid temperatures above 30°C (86°F).

5. Bio issues are pending.

6. There are no Patent or exclusivity issues pending.

Date of Review:
January 9, 1997

Date of Submission:
August 5, 1996

Primary Reviewer:
/S/

Date:
1/10/97

Secondary Reviewer:

Date:
1/10/97

Team Leader:
/S/

Date:
1/10/97

---

cc:

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-905

CORRESPONDENCE

TELEFAX DATED: July 14, 1997

ALTANA

Altana Inc. 60 Baylis Road, Melville, NY 11747 516-454-7677 Fax: 516-454-6369

BYK GULDEN PHARMA GROUP

TO: Mr. Joseph Buccine
Project Manager
Office of Generic Drugs (HFD-150)

FROM: Ms. Virginia Carman
Associate Director of Regulatory Affairs
Altana Inc.

OF PAGES (including this page): Three (3)

RE: ANDA 74-905 (Fluocinonide Ointment USP)

Dear Mr. Buccini:

As per our conversation of earlier today, here are the results of the first cycle study (4°C/45°C) done on the Reference Listed Drug Lidex.

As can be seen, although not all the data are failing, there is a definite trend towards that direction.

There are no specific questions that we wish to ask; we would like to discuss these results and their application to the assay results previously submitted for our product.

We would also like to note that the 24-month real time data, which were submitted in our fax amendment of April 4, 1997, are well within our stability specifications.

We appreciate your assistance in attempting to set up a conference call with Dr. Schwartz.

If there are any questions, please contact me at (516) 454-7677, Ext. 2091.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

/C/kmb

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Page(s) 2

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

7/14/97

stability data

Itana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-454-6389

ALTANA
BYK GULDEN PHARMA GROUP

FEDERAL EXPRESS

August 12, 1997

NEW CORRESP

Mr. Douglas L. Sporn
Director
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

RE: ANDA 74-905
Fluocinonide Ointment USP, 0.05%

Dear Mr. Sporn:

Reference is made to several teleconferences between Dr. Paul Schwartz, Dr. Allen Rudman, and Mr. Joseph Buccine of the OGD and Mr. Dave Pearce and Ms. Virginia Carman of Altana Inc. concerning the stability of our proposed product; specifically, the cycling studies.

We were requested to perform several additional studies on both the innovator product, Lidex Ointment (Hamilton), and our proposed product.

This information was originally faxed to the Office on July 14,1997 and August 6, 1997.

Both previously faxed submissions are included here as hard copy to the file.

If there are any questions, please contact me at (516) 454-7677, Ext. 2091.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

VC/kmb

Enclosures

RECEIVED
AUG 13 1997
GENERIC DRUGS

B:\LETTER\FLUOINT.812

TELEFAX DATED: August 6, 1997

ALTANA

Altana Inc 60 Baylis Road, Melville, NY 11747 516-454-7677 Fax: 516-454-6389

BYK GULDEN PHARMA GROUP

AMENDMENT

TO: Mr. Joseph Buccine
Project Manager
Office of Generic Drugs (HFD-150)

FROM: Virginia Carman
Associate Director
Regulatory Affairs
Altana Inc.

OF PAGES (including this page): 2

RE: ANDA 74-905 (Fluocinonide Ointment USP)

Dear Mr. Buccine

As per our conversation of earlier today, here are the results of the additional cycling study done on the Reference Listed Drug Lidex and our proposed drug product, which were requested by Dr. Paul Schwartz.

We trust that these data will alleviate any concerns regarding the stability of our drug product in comparison to the innovator's product.

If there are any questions, please contact me at (516) 454-7677 ext. 2091.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

C/ps

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ALTANA

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

FACSIMILE AMENDMENT

April 4, 1997

FPL
NEW CORRESP
NC

Mr. Douglas Sporn
Office of Generic Drugs
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 74-905
Fluocinonide Ointment USP, 0.05%

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application of May 23, 1996, as well as your facsimile deficiency notice of March 5, 1997.

We wish to respond to each point as follows:

A. **Deficiencies:**
Comment:

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

4/4/97

C. **Labeling Deficiencies:**

Comment:

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

   a. Revise storage recommendation to include, "Avoid temperature above 30°C (86°F)".

   b. Revise the "Each gram contains" statement to read, "Fluocinonide 0.5 mg solubilized...". (Delete "/g").

Response:

The container labeling has been revised as requested. Please see final printed container labeling in Attachment 6.

Comment:

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

   a. See CONTAINER comments.

   b. Revise "Each mL contains" to read, "Each gram contains".

Response:

Revised carton labeling may be found in Attachment 7.

Comment:

3. INSERT

a. DESCRIPTION

i. Revise the chemical name to read, "...9-difluoro...".

ii. Revise to include the molecular weight and molecular formula.

iii. Revise the second paragraph to read, "Each gram of Fluocinonide...".

iv. Revise the last sentence of the first paragraph to read, "...following structural formula:".

b. INDICATIONS AND USAGE

Revise to read, "... corticosteroid-responsive...".

c. PRECAUTIONS

i. GENERAL COMMENT

Please revise subsection headings to be consistent in format (e.g., italicized).

ii. General

Revise the first sentence of paragraph 3 to read, "Therefore, patients receiving a large...".

iii. Information for the patient

A. Make the following the first sentence of this subsection:

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

B. Delete the extra space between instruction 3 and 4.

C. Revise instruction 5 to read, "...diapers or plastic...".

iv. Carcinogenesis, Mutagenesis, and Impairment of Fertility

A. Revise to delete "and" in the subsection heading.

B. Revise the first sentence to read, "Long-term...".

C. Revise to let sentence 2 begin a new paragraph.

v. Pregnancy Category C

A. Revise the subsection heading to read:

Pregnancy. Teratogenic Effects.
Pregnancy Category C

B. Revise the penultimate sentence to read, "...potential benefit...".

C. Revise the ultimate sentence to read, "...patients, in large...".

vi. Pediatric Patients

Revise the penultimate sentence to read, "... to the least amount...".

d. DOSAGE AND ADMINISTRATION

Revise the ultimate sentence to read, "If an infection...".

e. HOW SUPPLIED

Revise the storage recommendations to read, "Store at controlled room temperature 15° - 30°C (59° - 86°F). Avoid temperature above 30°C (86°F).

Response:

Revised insert labeling which incorporates all of the Division's changes is included in Attachment 8.

As requested, side by side comparisons of the proposed labeling and that of the last submission may be found in Attachment 9 (container), Attachment 10 (carton), and Attachment 11 (insert).

We certify that an exact copy of this facsimile amendment has been submitted to the local district office.

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

Sincerely,

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

VC/kmb

Enclosures

ALTANA

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

FEDERAL EXPRESS

[illegible] CORRESP

NC

April 3, 1997

Mr. Douglas Spom
Office of Generic Drugs
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 74-905
Fluocinonide Ointment USP, 0.05%

Dear Mr. Spom:

Reference is made to our ANDA filed August 6, 1996. Reference is also made to our telephone conversations with the Division of Bioequivalence (DOB) of February 24, 1996; February 28, 1996; and March 5, 1996.

As a result of the March 5, 1996 discussion, information was submitted concerning the demographics of the population enrolled in the pivotal study. We indicated then that the data for the pilot study would be forwarded as soon as it became available.

The pilot study demographics data is included with this letter.

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

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

VC/kmb

Enclosure

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TELEFAX DATED: April 4, 1997

ALTANA

Altana Inc. 60 Baylis Road, Melville, NY 11747 516-454-7677 Fax 516-454-6389

BYK GULDEN PHARMA GROUP

TO: Document Control Room, Metro Park North II
Office of Generic Drugs

FROM: Ms. Virginia Carman
Altana Inc.

NDA ORIG AMENDMENT
N/FA

OF PAGES (including this page): 42

RE: **ANDA 74-905**
Fluocinonide Ointment USP, 0.05%
FACSIMILE AMENDMENT

Dear Sir:

Reference is made to your facsimile of March 5, 1997 containing five (5) pages of minor deficiencies and comments. Reference is also made to my telephone conversation of April 3 with Mr. Mark Anderson verifying the date by which this must be responded to.

The following submission contains a complete response to all of the chemistry issues.

Because of the amount of labeling, the size of print and color of tubes, we have not faxed copies of the final printed labeling. This will be submitted in the hard copies which are being sent by Federal Express today.

There are 42 pages including this cover sheet. If there is any problem in the receipt of this fax, please call me at (516) 454-7677, Ext. 2091.

Thank you for your assistance.

Sincerely,

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

VC/kmb

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#35 97 sub

ANDA 74-905

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

MAY 30 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Fluocinonide Topical Ointment USP, 0.05%.

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

ADDITIONAL COMMENT:

All AUEC values reported were not correct, and the evaluation of bioequivalence was based on values calculated by the reviewer. The spreadsheets submitted in electronic formats did not contain the AUEC formula. In the future, this method of calculation of AUEC should be corrected, and accompanied by spreadsheets containing formulae used for all calculations.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ALTANA

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

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FEDERAL EXPRESS

March 5, 1997

Mr. Douglas Sporn
Office of Generic Drugs
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 74-905
Fluocinonide Ointment USP, 0.05%

NEW CORRESP

Dear Mr. Sporn:

Reference is made to our ANDA filed August 6, 1996. Reference is also made to several telephone conversations of February 24, 1996, February 28,1996, and March 5, 1996 with the Division of Bioequivalence (DOB), as well as, the submission of a computer diskette to the DOB on February 26, 1997.

As requested on February 28, enclosed you will find a PC formatted disk containing the study information, as well as a letter from Dr. Lynn Pershing, the Study Director containing information to assist the Division in reading the disk.

Also, as per the conversation of March 5, 1997 the batch size of Fluocinonide Ointment Lot #6445 used in the bioequivalence study was 200 kg.

Page 305 of the original application contained the demographics questionnaire for the pivotal study. As can be seen, weight was not requested. However, age, gender, and race were. Page 306 contained this information for the pivotal trial.

Those pages are included herein.

The remaining information on the pilot study will be faxed to you as soon as it becomes available.

If any other information is requested, please contact me at (516) 454-7677 Ext. 2091.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

VC/kmb

Enclosures

RECEIVED
MAR 06 1997
GENERIC DRUGS

ALTANA

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

NEW CORRESP.

BIOAVAILABILITY

NC 18TO

FEDERAL EXPRESS

February 26, 1997

Mr. Douglas Sporn
Office of Generic Drugs
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 74-905
Fluocinonide Ointment USP, 0.05%

Dear Mr. Sporn:

Reference is made to our abbreviated New Drug Application filed August 6, 1996. Reverence is also made to a telephone request of February 24, 1997 from the Division of Bioequivalence for a copy of the Bioequivalence data in disk format.

As requested, you will find a PC Disk formatted for Excel containing the pilot and pivotal study data.

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

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

VC/kmb

Enclosure

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RECEIVED
FEB 27 1997
GENERIC DRUGS

ANDA 74-905

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

SEP 13 1996

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated July 17, 1996, and your amendment dated August 5, 1996.

NAME OF DRUG: Fluocinonide Ointment USP, 0.05%

DATE OF APPLICATION: May 23, 1996

DATE OF RECEIPT: May 24, 1996

DATE ACCEPTABLE FOR FILING: August 6, 1996

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Bill Russell
Project Manager
(301) 594-1841

Sincerely yours,

/S/ 3/96

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

505(j)(2)(a) info acceptable for filing
8/16/96 Ann Marie H. Waite

ALTANA

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

BYK GULDEN PHARMA GROUP

Federal Express

8/19/96
CP

August 5, 1996

NDA ORIG AMENDMENT
N/AC

Mr. Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Metro Park North II, HFD-617, Room 237N
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

RECEIVED
AUG 6 1996
GENERIC DRUGS

Re: ANDA 74-905
Fluocinonide Ointment USP, 0.05%

Dear Mr. Phillips:

Reference is made to your communication of July 17, 1996, indicating the Office of Generic Drugs' reasons for refusing to file our application.

Your letter states:

Comment:

You have failed to provide a side-by-side comparison of the formulation of your proposed drug product with that of the reference listed drug product. You must demonstrate that the proposed drug product is qualitatively and quantitatively the same as the reference listed drug product. In addition, if any qualitative or quantitative differences do exist between your proposed drug product and the reference listed drug, you must provide information to demonstrate these differences do not affect the safety of the proposed drug product [21 CFR 314.94 (a) (9) (v)].

The information to demonstrate safety should include, but is not limited to: (a) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients and that are within the same concentration range, (b) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (c) a comparison of the physical and chemical properties (e.g. pH, viscosity partition coefficient) of the proposed drug

product with that of the reference listed drug, and (d) information to show that the inactive ingredients do not adversely affect these properties.

Response:

We acknowledge that we did not provide a side-by-side quantitative comparison between our product and the reference listed drug product, however, a qualitative statement was made in Section 7.

The quantitative composition of Lidex Ointment (Hamilton Pharma CA) was determined analytically and our product was formulated to be quantitatively identical to it. A report on the development of this product is included in Attachment 1.

As our product is qualitatively and quantitatively identical to the reference listed drug, Lidex, there are no issues regarding the safety of the drug product's formulation.

Comment:

While we note you have provided a packaging summary, you have failed to provide complete packaging recordings for each container size including reconciliation records. Please provide complete packaging records. Please refer to The Office Generic Drugs, Policy & Procedure Guide #41-95 for guidance on the packaging of test batches.

Response:

After your comment was received, the batch record was pulled and reviewed against the information sent to you. It was noticed that indeed, during the copying process several pages were inadvertently omitted. Attachment 2 contains a complete copy of the batch record. The records for each package size, 15, 30 and 60 grams are grouped together for ease of review. The last page of the batch record contains the reconciliation.

Comment:

Your blank master batch records fail to include master packaging records. Please be aware that a batch is not considered processed until it has been completely packaged. Please provide blank master packaging records.

Response:

Attachment 3 contains copies of blank master packaging records. Please note that the "packaging qualification record" which is found in the submitted batch, 6445 is an R & D form only and is not routinely used in manufacturing, it is therefore not included.

We also wish to respond to the following comment concerning labeling:

Comment:

In addition, while we note that you have provided side-by-side labeling comparisons with differences noted, you failed to annotate these differences. Please provide a side-by-side comparison of your proposed labeling with the approved labeling for the reference listed drug product with all differences annotated and explained [21 CFR 314.94 (a) (8) (iv)].

Response:

A side by side comparison was submitted with the differences explained in the center column.

We are resubmitting the labeling, which has been revised to highlight each statement or section that is being changed. The center panel will continue to annotate the changes that have been made to the innovator labeling.

We respectfully request, that with the addition of the enclosed information, our application for Fluocinonide Ointment USP 0.05% be accepted for filing.

Sincerely,
Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

VC:ch

encls.

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