CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74905

Trade Name Fluocinonide Ointment USP 0.05%

Generic Name Fluocinonide Ointment USP 0.05%

Sponsor Altana, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74905

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	Included	Pending Completion	Not Prepared	Not Required
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Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
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Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74905

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,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

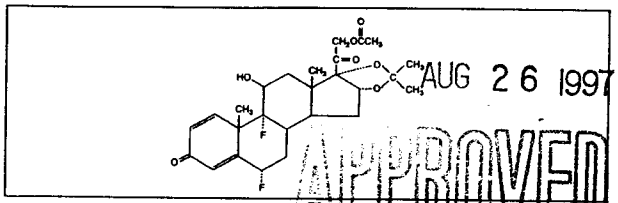
APPLICATION NUMBER 74905

FINAL PRINTED LABELING

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

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

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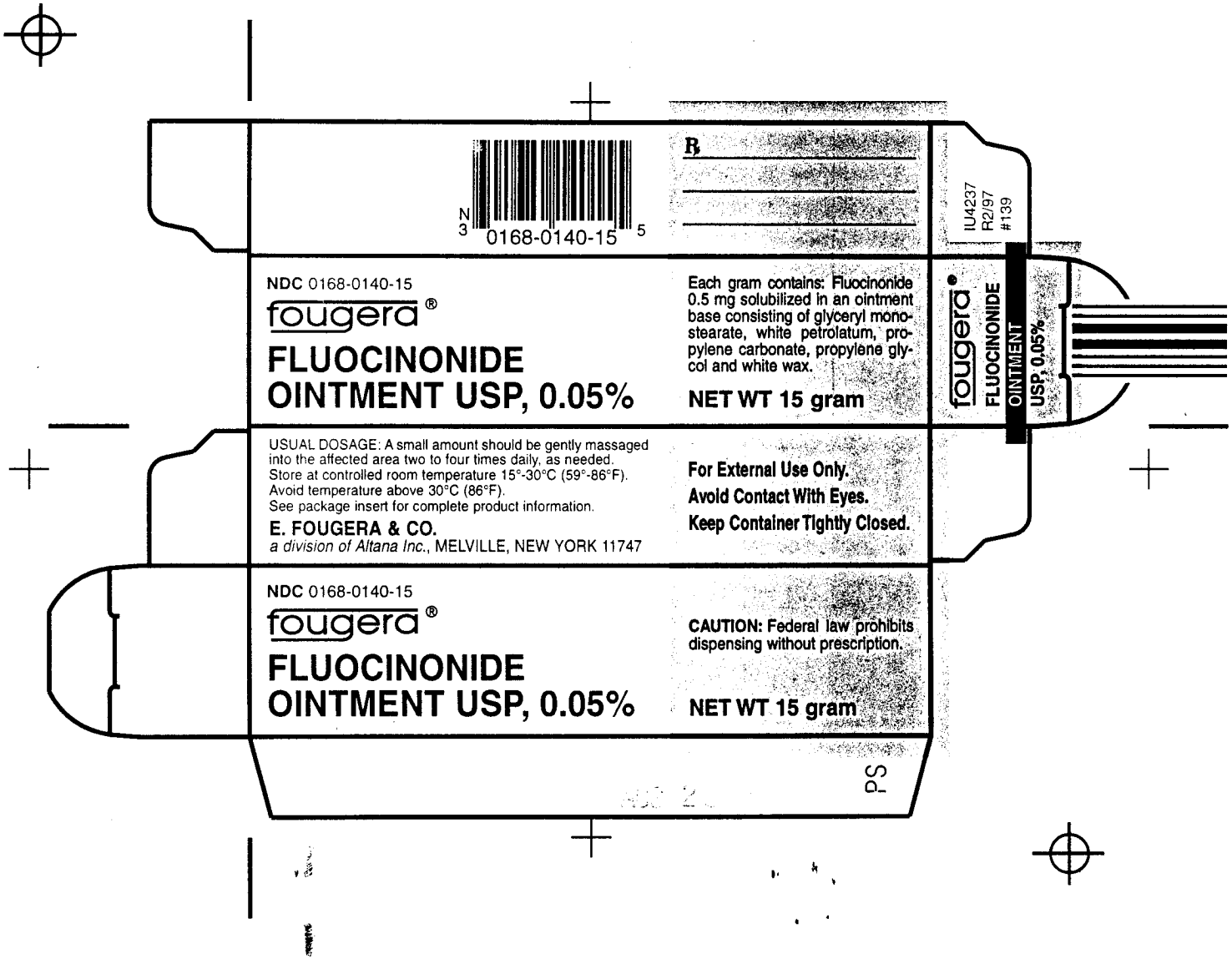
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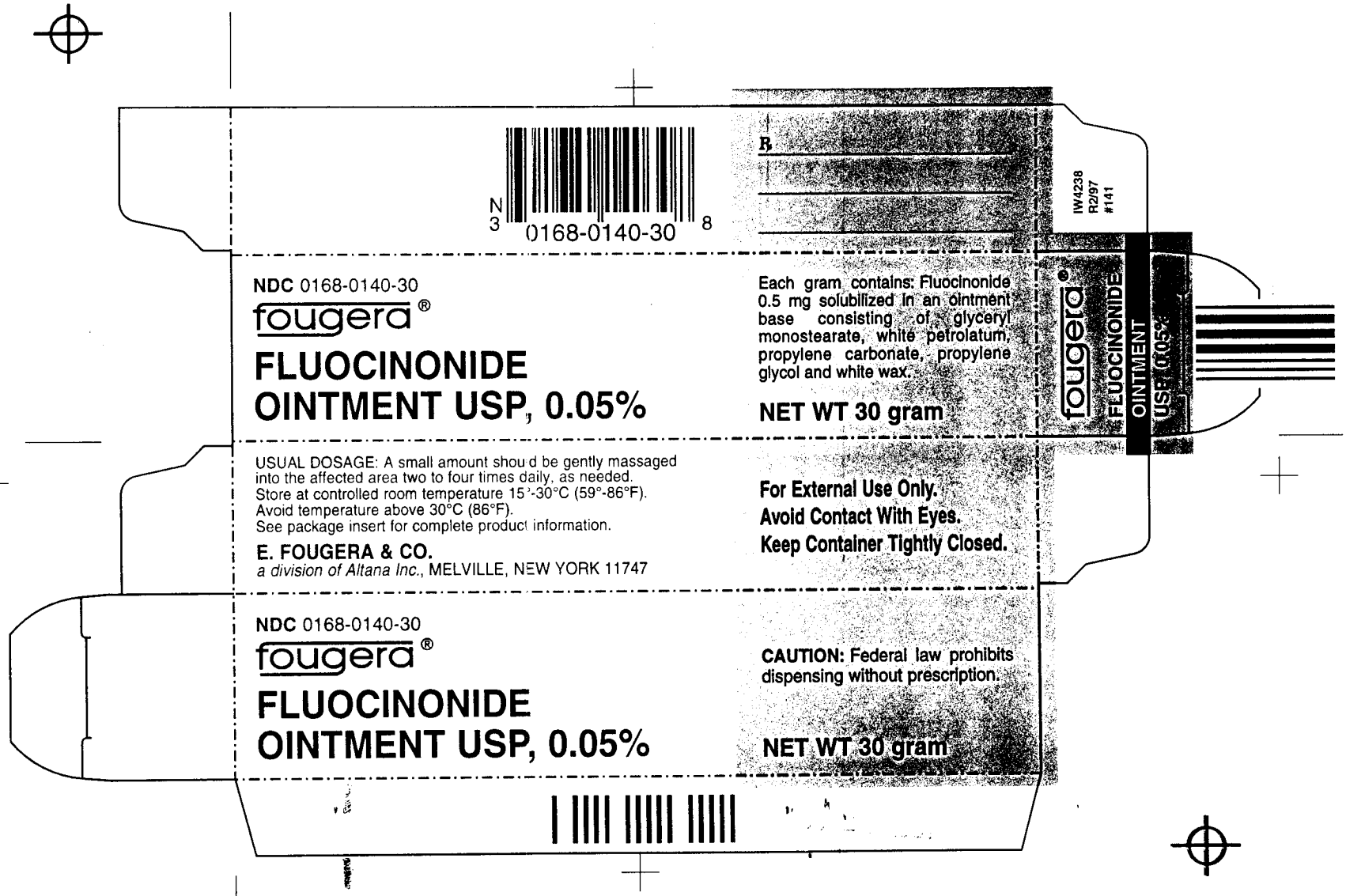
IU4237
R2/97
#139
NDC 0168-0140-15
fougera®
FLUOCINONIDE
OINTMENT USP, 0.05%
Each gram contains: Fluocinonide 0.5 mg solubilized in an ointment base consisting of glyceryl monostearate, white petrolatum, propylene carbonate, propylene glycol and white wax.
NET WT 15 gram
fougera®
FLUOCINONIDE
OINTMENT
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
For External Use Only.
Avoid Contact With Eyes.
Keep Container Tightly Closed.
NDC 0168-0140-15
fougera®
FLUOCINONIDE
OINTMENT USP, 0.05%
CAUTION: Federal law prohibits dispensing without prescription.
NET WT 15 gram
PS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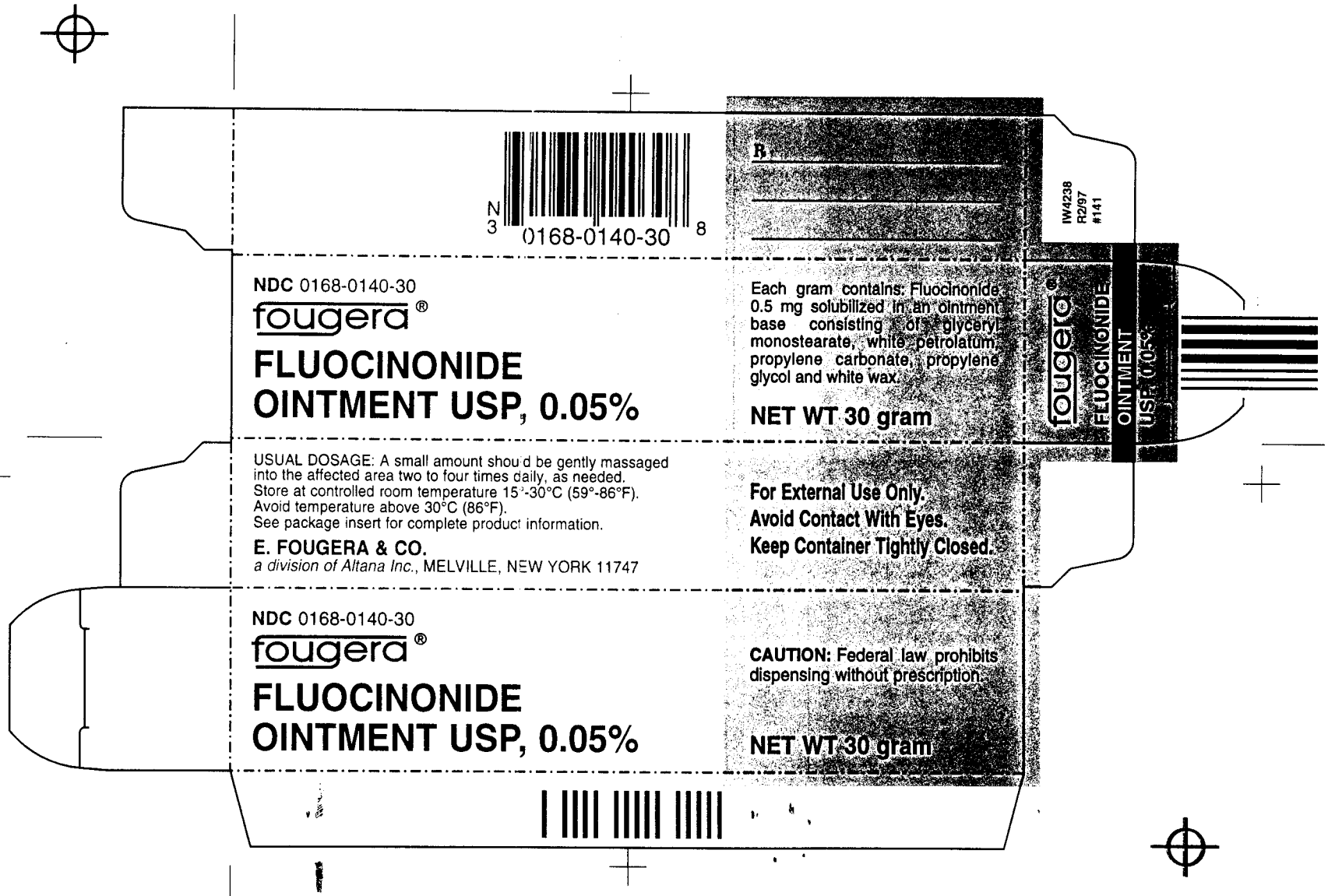
R2/97
#141
NDC 0168-0140-30
fougera®
FLUOCINONIDE
OINTMENT USP, 0.05%
Each gram contains: Fluocinonide 0.5 mg solubilized in an ointment base consisting of glyceryl monostearate, white petrolatum, propylene carbonate, propylene glycol and white wax.
NET WT 30 gram
fougera®
FLUOCINONIDE
OINTMENT
USP 0.05%
USUAL DOSAGE: A small amount shou d 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
For External Use Only.
Avoid Contact With Eyes.
Keep Container Tightly Closed.
NDC 0168-0140-30
fougera®
FLUOCINONIDE
OINTMENT USP, 0.05%
CAUTION: Federal law prohibits dispensing without prescription.
NET WT 30 gram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#141
NDC 0168-0140-30
fougera®
FLUOCINONIDE
OINTMENT USP, 0.05%
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 30 gram
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
For External Use Only.
Avoid Contact With Eyes.
Keep Container Tightly Closed.
fougera®
FLUOCINONIDE
OINTMENT USP, 0.05%
CAUTION: Federal law prohibits dispensing without prescription.
NET WT 30 gram

SHOULDER
TUBE LENGTH 4"
B.M. 1/8"
OPEN END
2 9/32 CIRCUMFERENCE
NDC 0168-0140-15
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 15 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.
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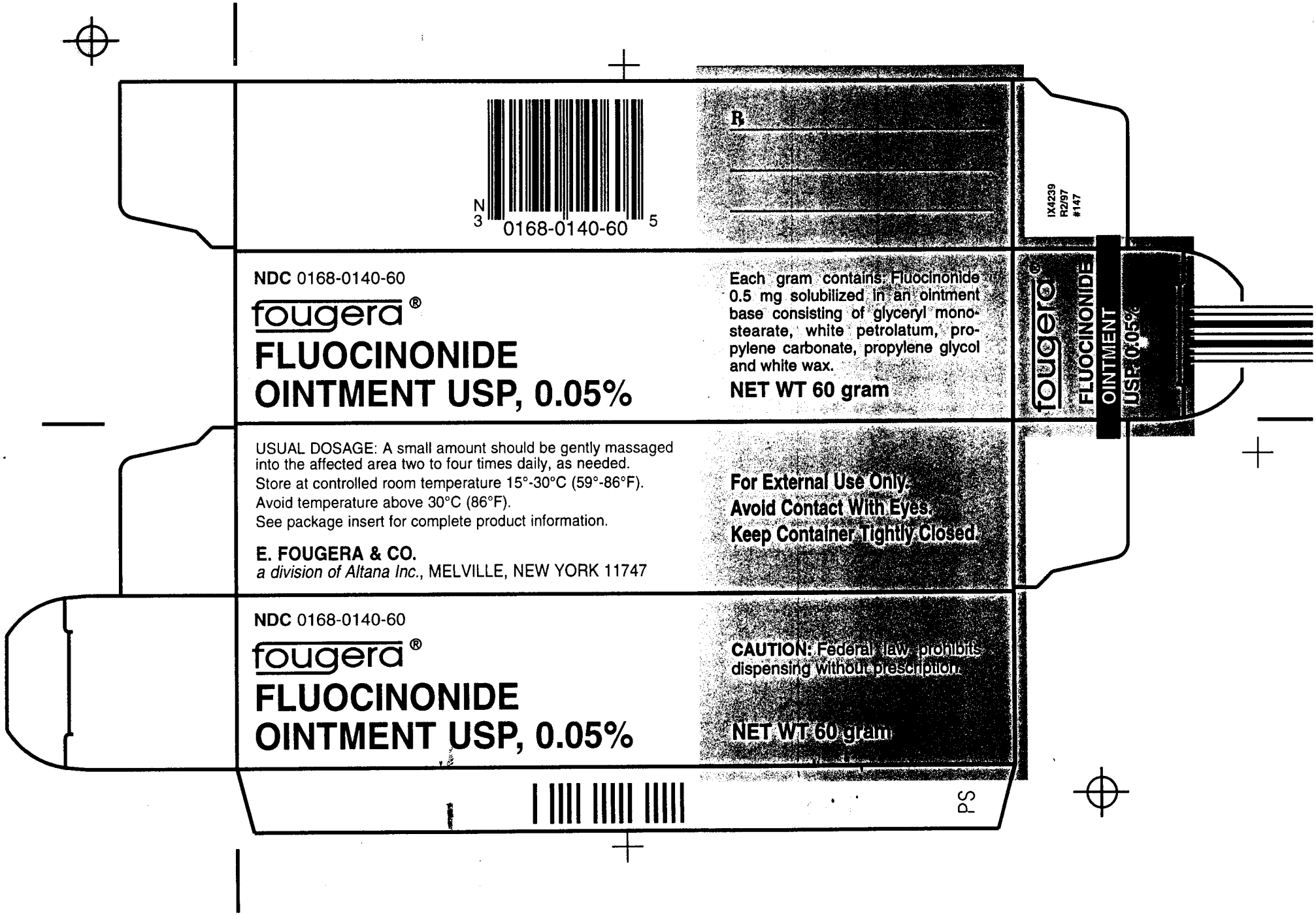
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IX4239
R2/97
#147
NDC 0168-0140-60
fougera®
FLUOCINONIDE
OINTMENT USP, 0.05%
Each gram contains: Fluocinonide 0.5 mg solubilized in an ointment base consisting of glyceryl monostearate, white petrolatum, propylene carbonate, propylene glycol and white wax.
NET WT 60 gram
fougera®
FLUOCINONIDE
OINTMENT
USP 0.05%
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
For External Use Only.
Avoid Contact With Eyes.
Keep Container Tightly Closed.
NDC 0168-0140-60
fougera®
FLUOCINONIDE
OINTMENT USP, 0.05%
CAUTION: Federal law prohibits dispensing without prescription.
NET WT 60 gram
PS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74905

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:

8/11/97

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

Supervisor: Paul Schwartz, Ph.D.

cc: ANDA 74-905
Division File
Field Copy

Endorsements:
HFD-627/N.Nashed, Ph.D./
HFD-627/P.Schwartz, Ph.D./
X:\NEW\FIRMSAM\ALTANA\LTRS&REV\74-905.2
F/T by: bc/6-9-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74905

BIOEQUIVALENCE REVIEW(S)

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,

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

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., and Of these two chromameters, the instruments 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 0.8% - 10.8% (pp 90, vol 1.1). Similarly %CV for ointment application ranged from 0.3% - 10%.

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 Institutional 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: 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 reviewer. 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 $AUEC_{0-24}$ 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 91%-116%.

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 99% - 129%.

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%
Glyceryl Monostearate White Wax White Petrolatum Propylene Glycol Propylene Carbonate		

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 Glyceryl Stearate in the reference product, instead of Glyceryl *Mono*stearate 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.

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

RD INITIALE
FT INITIALEI

CONCUR: _
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence.

GJP SINGH 3-19-97/74905S.596 (Review start date: February 24, 1997).
cc. ANDA # 74905, original, HFD-630 (OGD), HFC-130 (Jallen), HFD-600 (Hare), HFD-655 (Nerurkar, Singh), Drug file, Division file.

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

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		
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)

	AUEC (0-24)	
Sub	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	Sub	AUEC (0-24) TEST	AUEC (0-24) REF
1			31		
2			32		
3			33		
4			34		
5			35		
6			36		
7			37		
8			39		
9			40		
10			41		
11			42		
12			43		
13			44		
14			45		
15			46		
16			47		
17			48		
18			49		
19			50		
20			51		
21			52		
22			53		
23			54		
24					
25			mean	38.30	36.86
27			SD	16.36	17.55
28			CV%	43	48
29					
30					

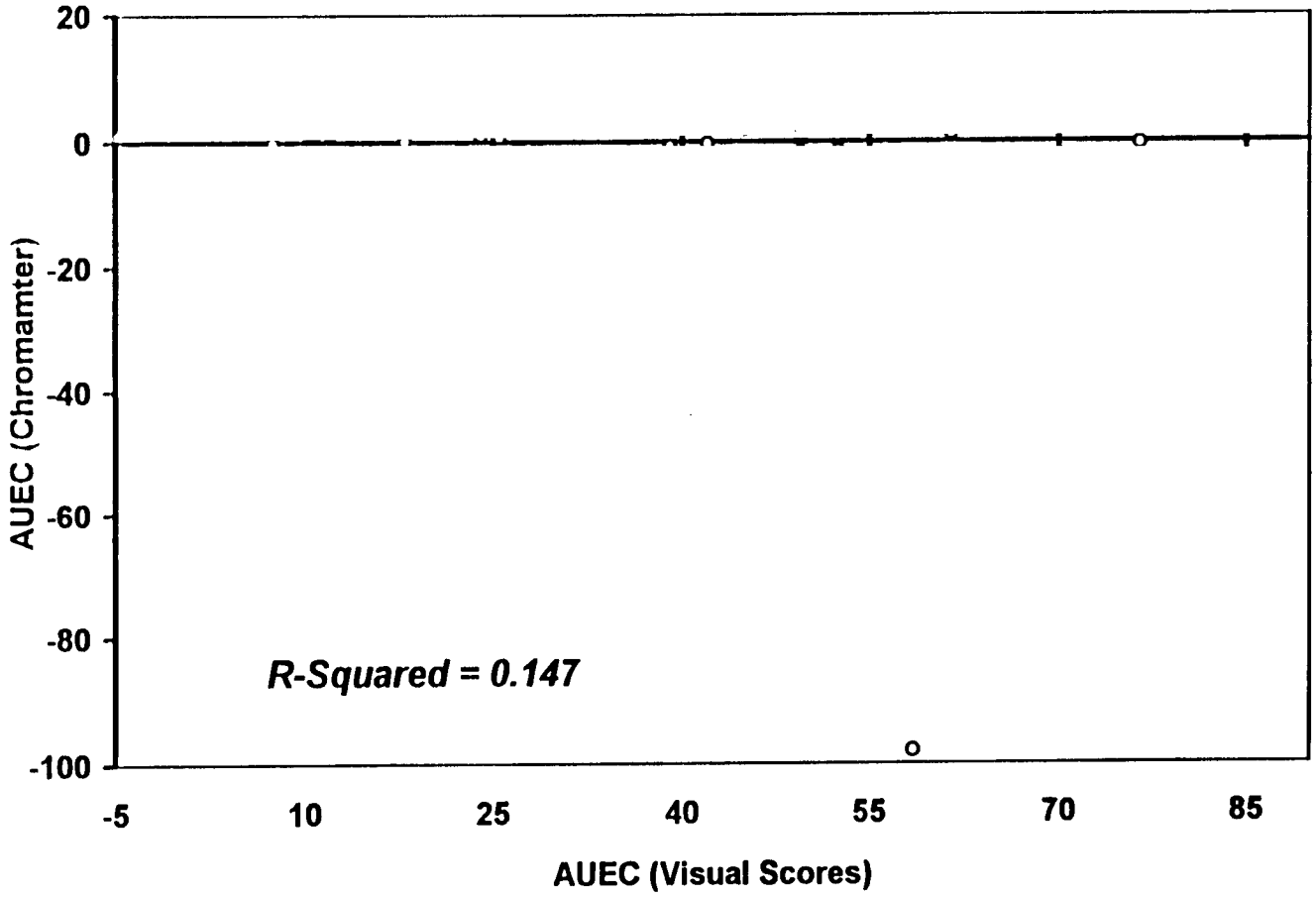
Highlighted cells indicate test and reference products' data used for bioequivalence comparisons

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	36.10	32.11
SD	15.27	16.42
CV%	42	51

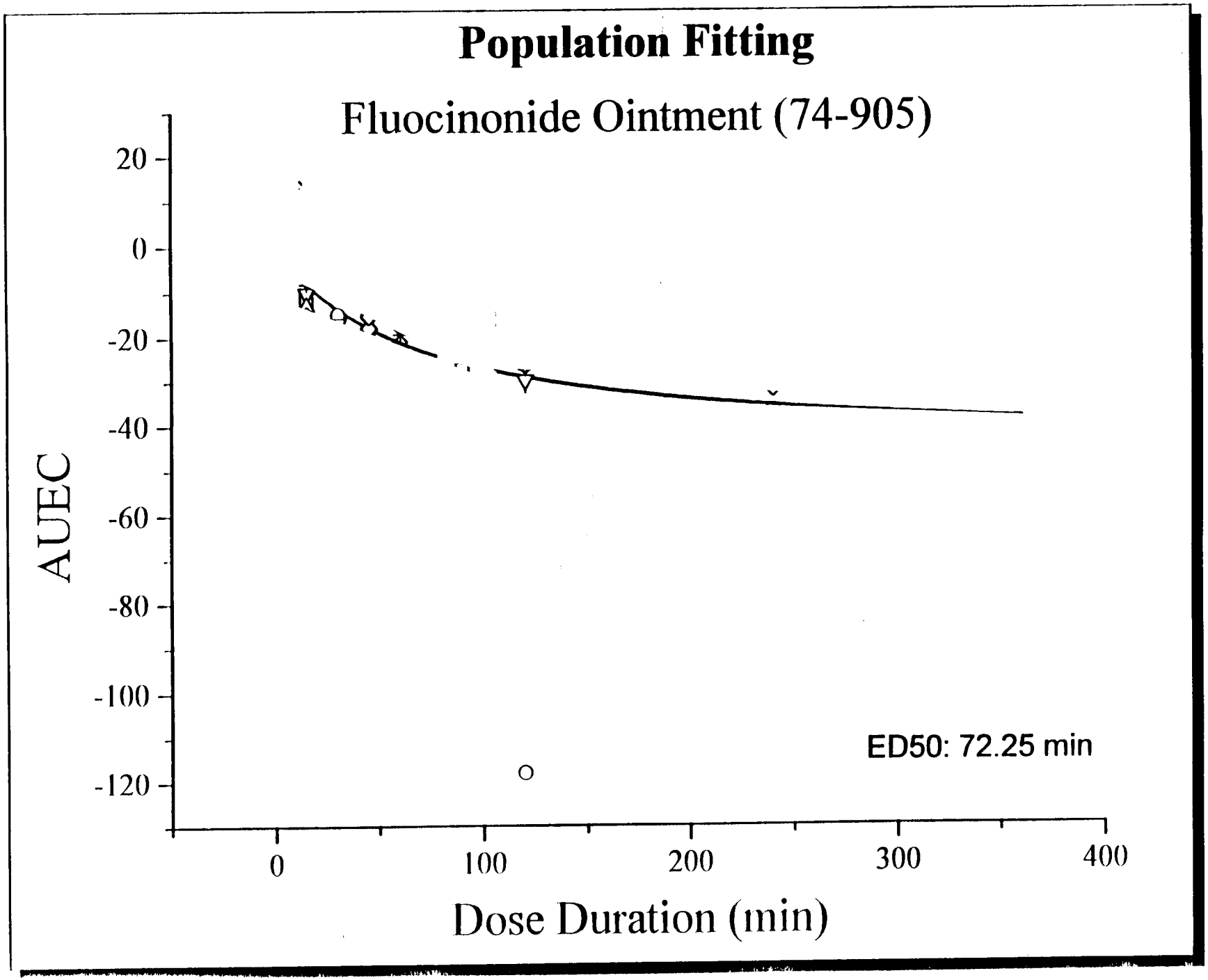
Note: The sponsor included subjects #10 for confidence interval calculations. The reviewer has excluded that subject because its D2/D1 ratio is 0.75. The sponsor has reported the same D2/D1 ratio for this subject (pp 747, vol. 1.2)

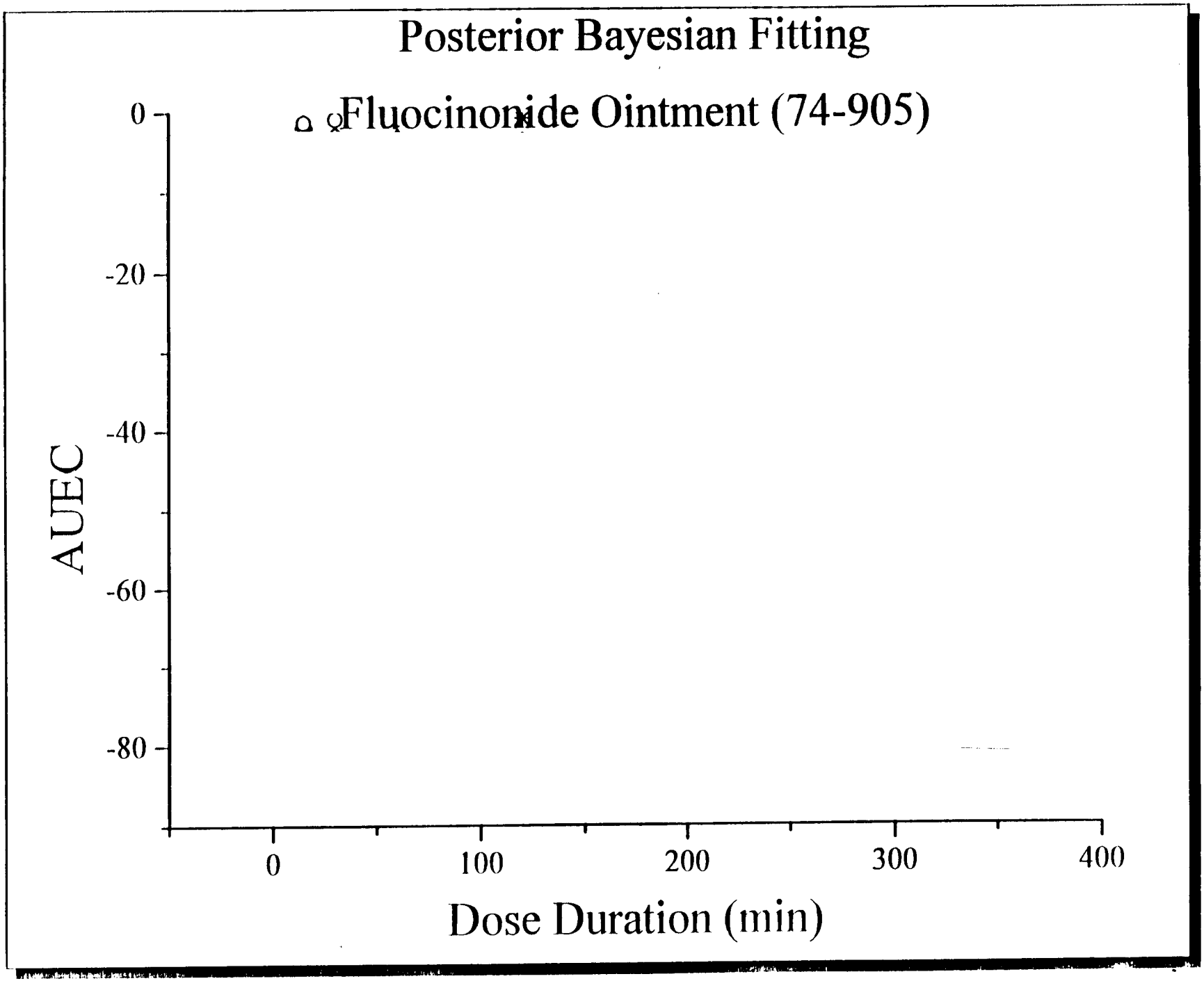
Figure 1. Correlation between AUEC (0-24) values based on chromameter data and visual scores (ANDA #74-905)

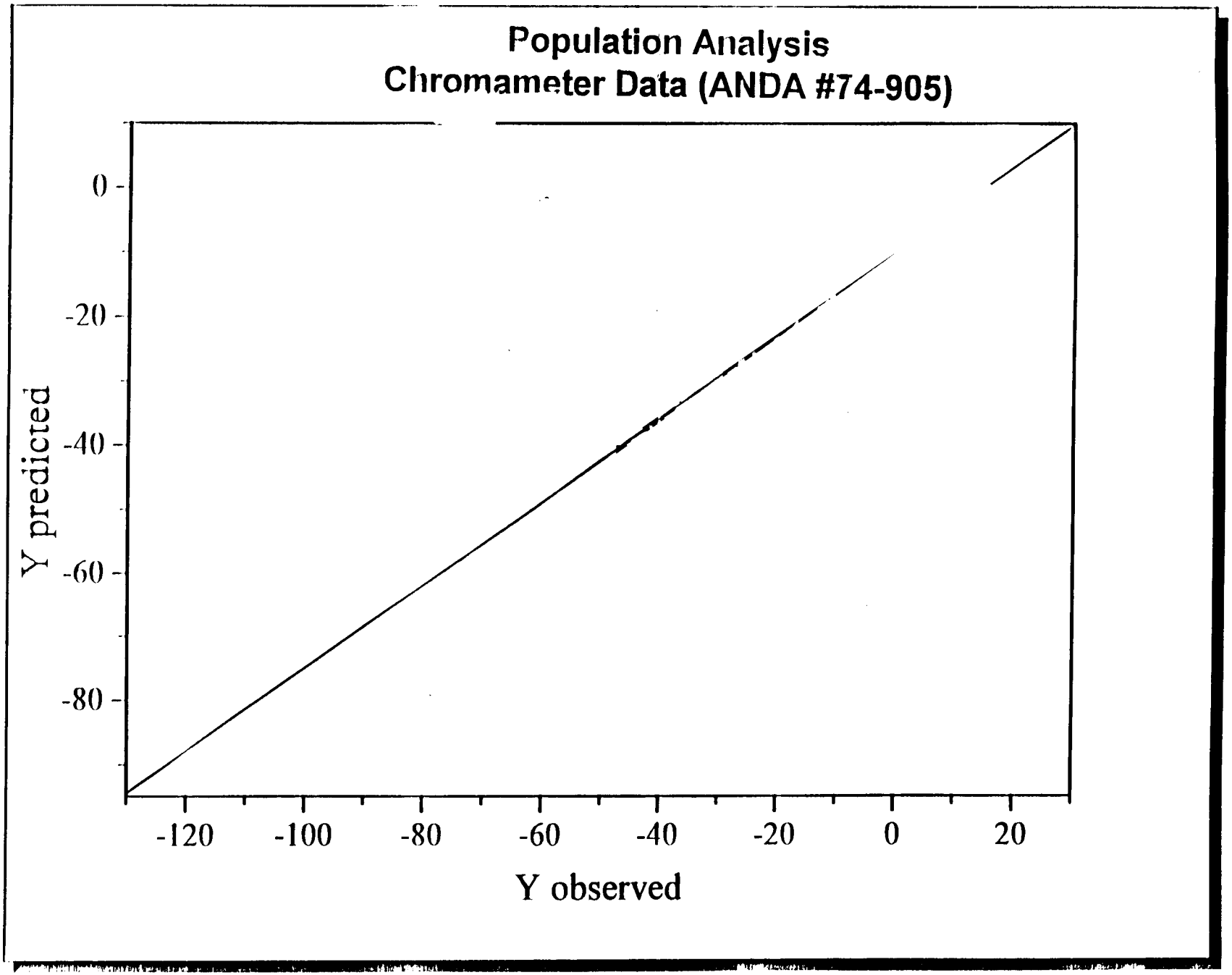


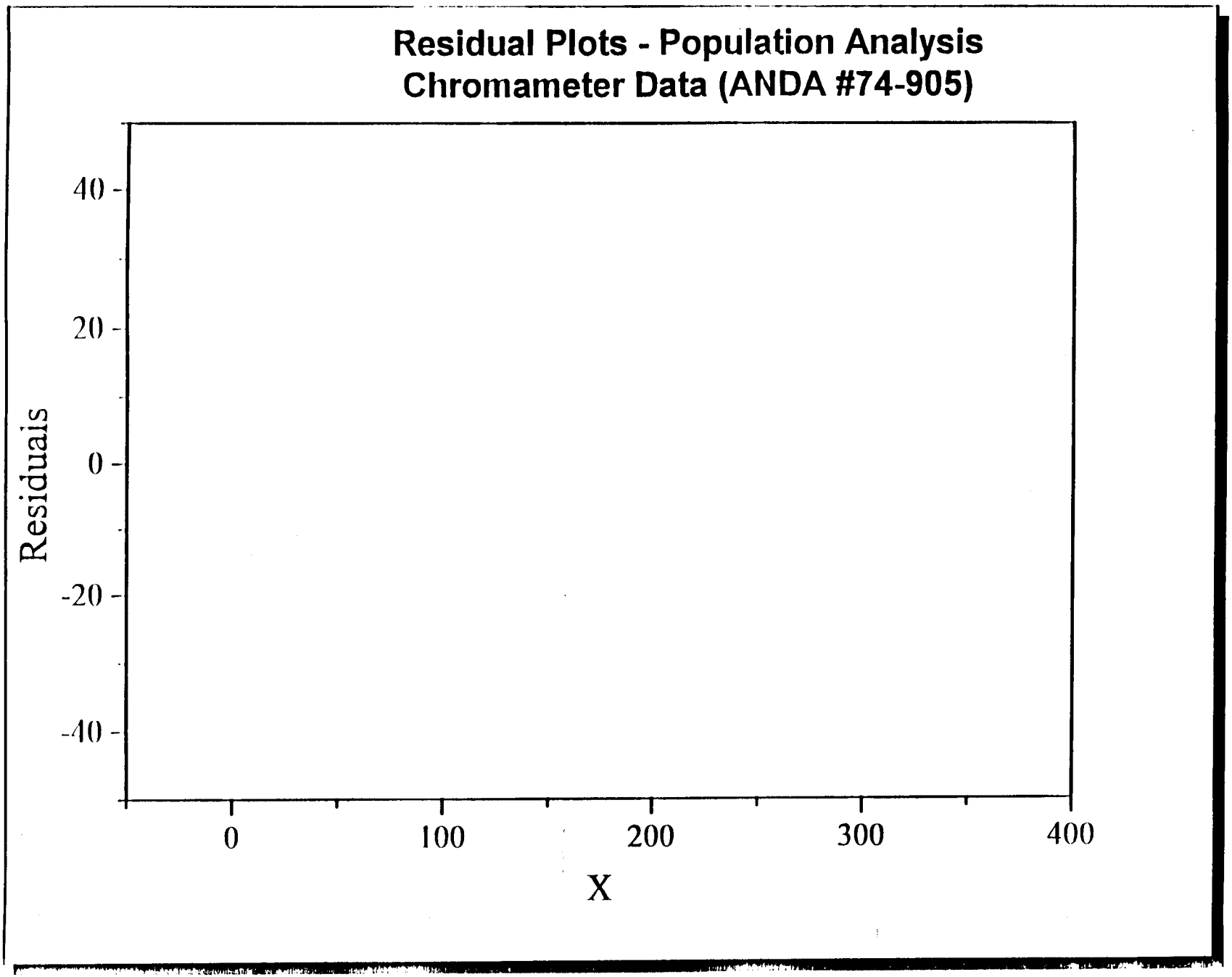
APPENDIX 1

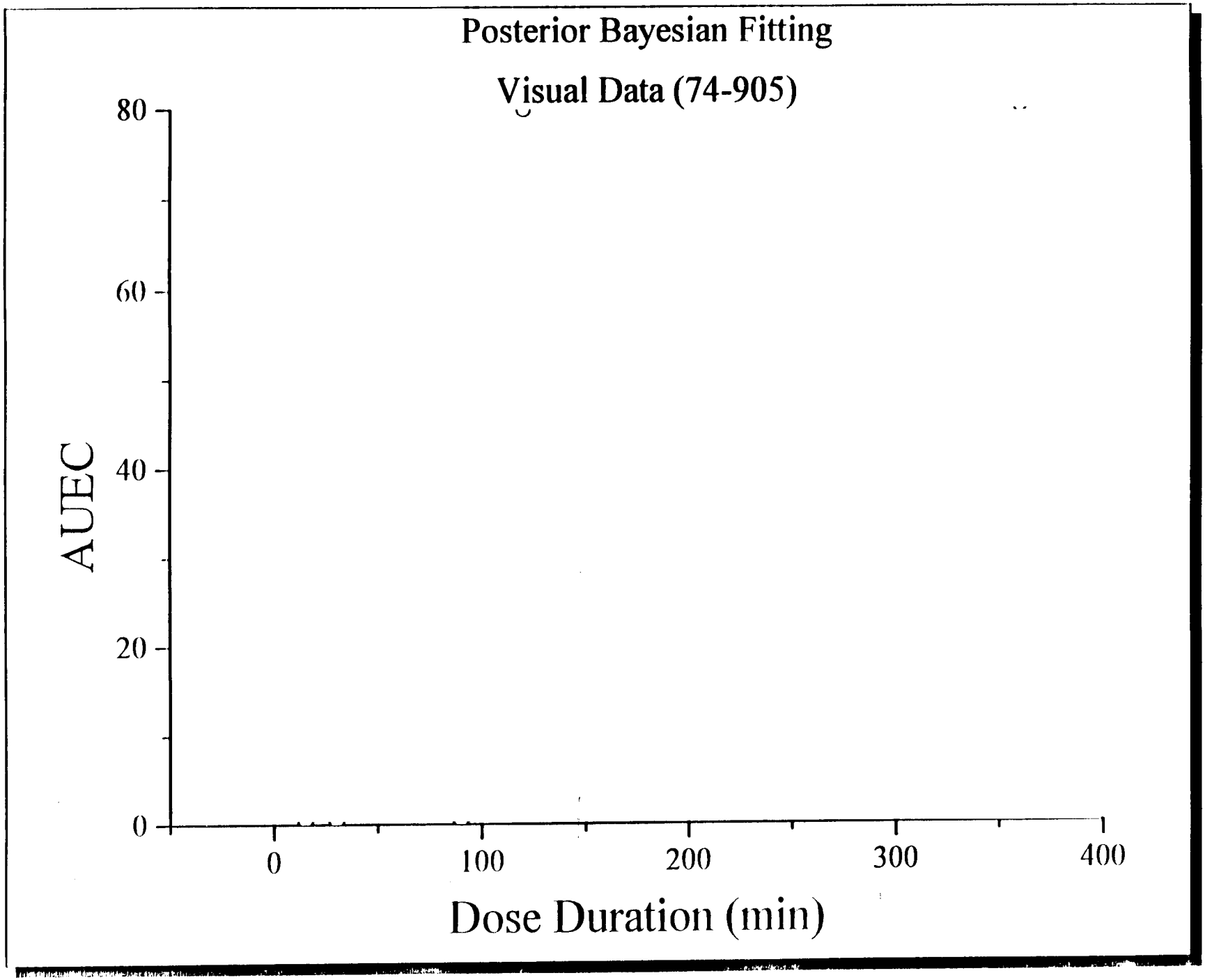
Nonlinear Mixed Effect Modeling of the Pilot Study Data

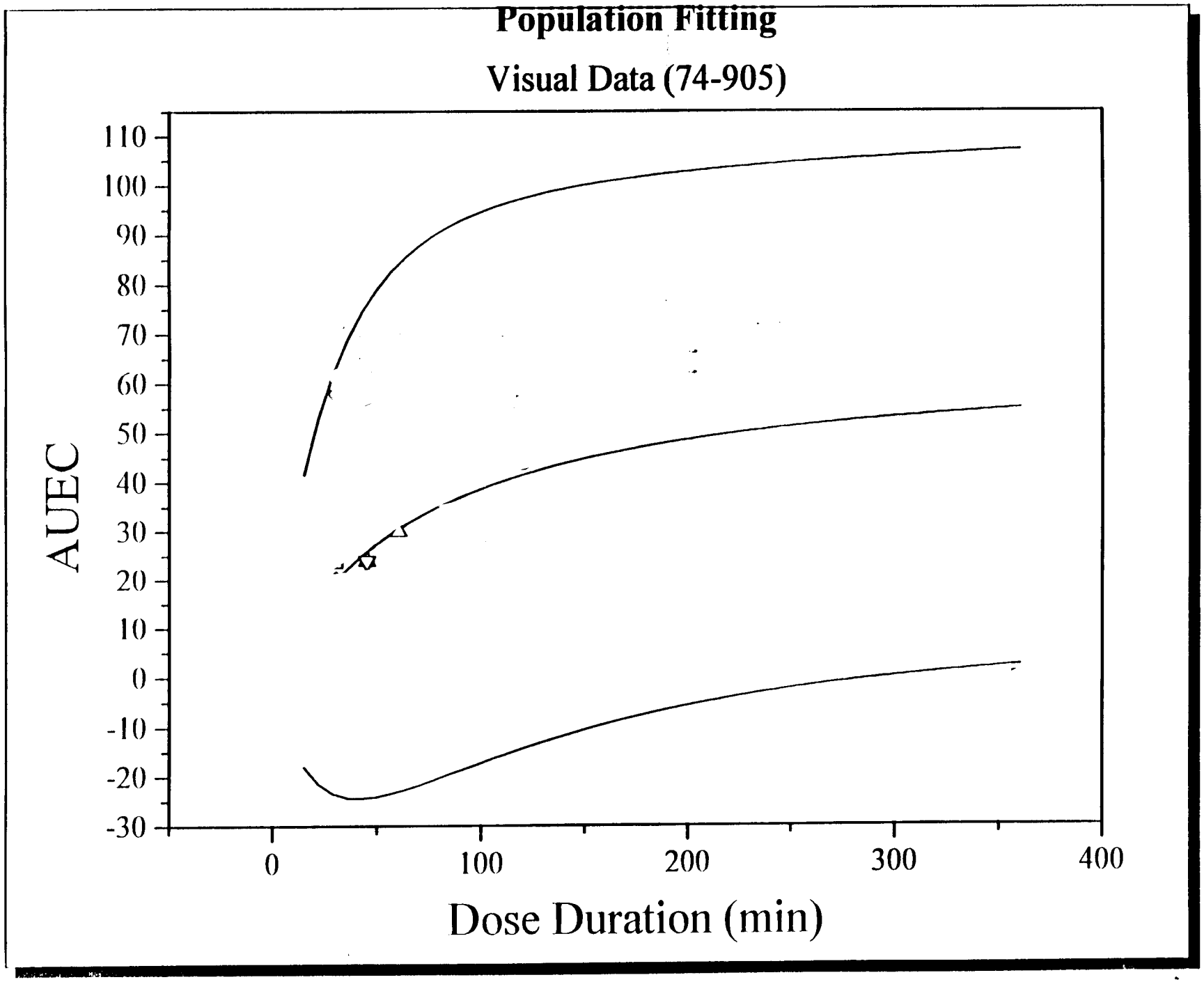

Population Fitting
Fluocinonide Ointment (74-905)
AUEC
20
0
-20
-40
-60
-80
-100
-120
0
100
200
300
400
Dose Duration (min)
ED50: 72.25 min

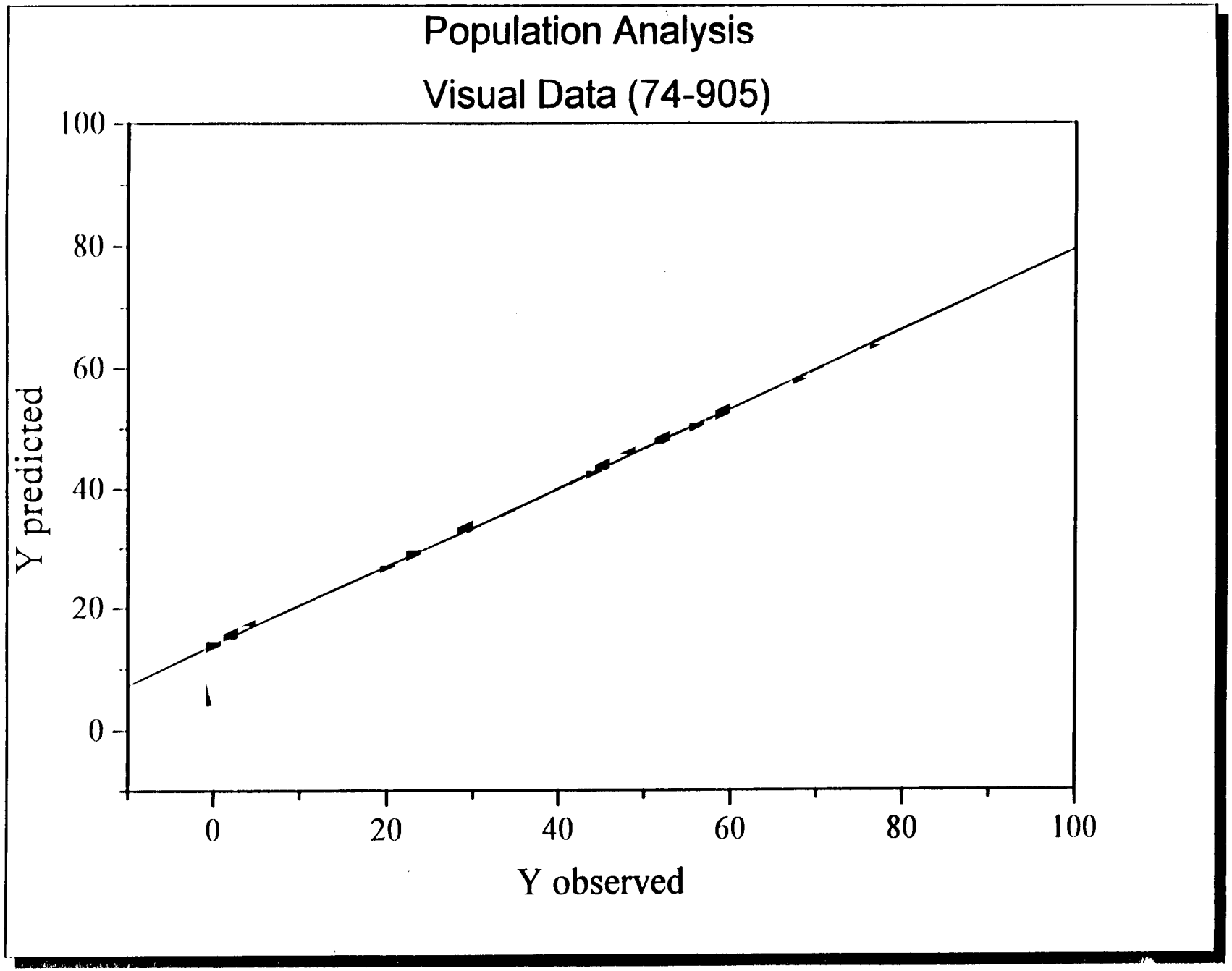

Posterior Bayesian Fitting
Fluocinonide Ointment (74-905)
AUEC
0
-20
-40
-60
-80
0
100
200
300
400
Dose Duration (min)

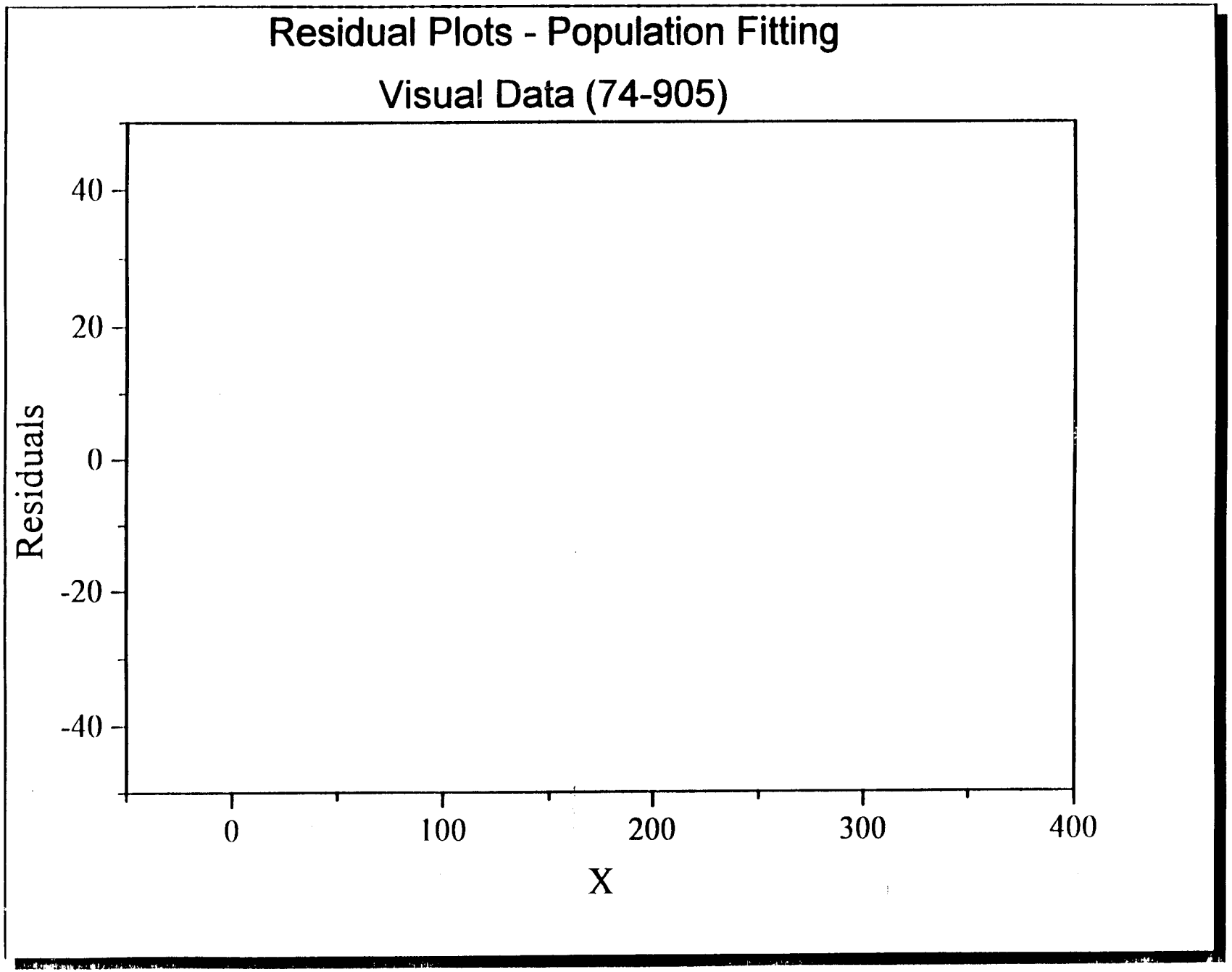

Population Analysis
Chromameter Data (ANDA #74-905)
0
-20
-40
-60
-80
Y predicted
-120
-100
-80
-60
-40
-20
0
20
Y observed


Residual Plots - Population Analysis
Chromameter Data (ANDA #74-905)
Residuais
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
100
80
60
40
20
0
0
20
40
60
80
100
Y observed


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