CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-751

APPROVAL LETTER

ANDA 75-751

MAR 12 2001

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

Dear Madam:

This is in reference to your abbreviated new drug application dated December 7, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Desonide Ointment, 0.05%.

Reference is also made to your amendments dated March 29, June 26, and November 1, 2000; and February 28, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Desonide Ointment, 0.05% to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Tridesilon® Topical Ointment, 0.05% of Clay Park Laboratories Inc.).

Under Section 506A of the Act, 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 and 314.98. 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-40). 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-40) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

Gary Buehler 3/12/01

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-751

APPROVED DRAFT LABELING

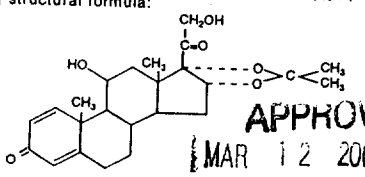
fougera®

DESONIDE OINTMENT, 0.05%

℞ only

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

DESCRIPTION: Desonide Ointment, 0.05% contains microdispersed desonide (the active ingredient) in white petrolatum. Each gram of desonide ointment contains 0.5 milligrams of desonide. Desonide Ointment is applied topically. Desonide is a non-fluorinated corticosteroid. Chemically, desonide is pregna-1,4-diene-3,20-dione, 11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-, (11β,16α)- with the following structural formula:



APPROVED
MAR 12 2001

Molecular Formula $C_{24}H_{32}O_6$ Molecular Weight 416.51 CAS Registry No: 638-94-8

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

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.
Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses. (See **DOSAGE AND ADMINISTRATION**).

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. 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: Topical corticosteroids are 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 areas, prolonged use, and the addition of occlusive dressings. Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.
Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.
Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See **PRECAUTIONS - Pediatric Use.**)
If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

(over)

2

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 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 a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use: *Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.*
Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in 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: Topical corticosteroids are generally applied to the affected area as a thin film from two to three 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: Desonide Ointment, 0.05% is supplied in 15 and 60 gram tubes. It is white or faintly yellowish, transparent semisolid.

15 gram tubes, NDC 0168-0309-15
60 gram tubes, NDC 0168-0309-60

Store below 30°C (86°F). Avoid freezing.

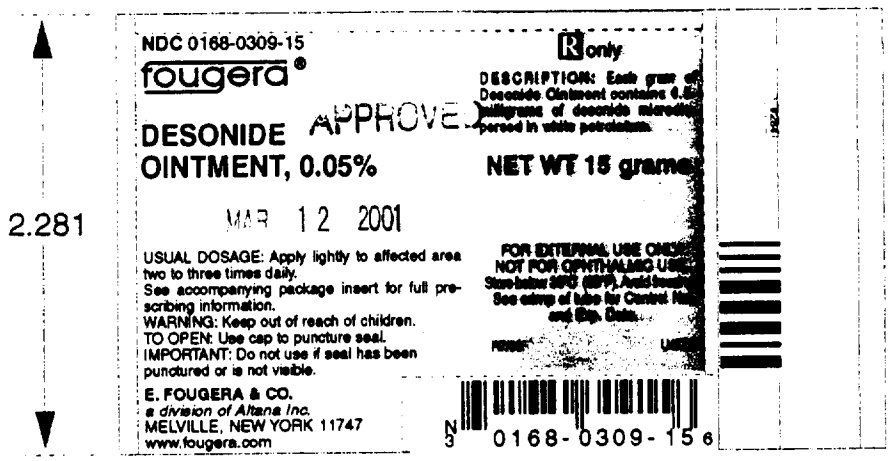
E. FOUGERA & CO.
a division of Altana Inc.
MELVILLE, NEW YORK 11747
www.fougera.com

I2309
R7/00
#284

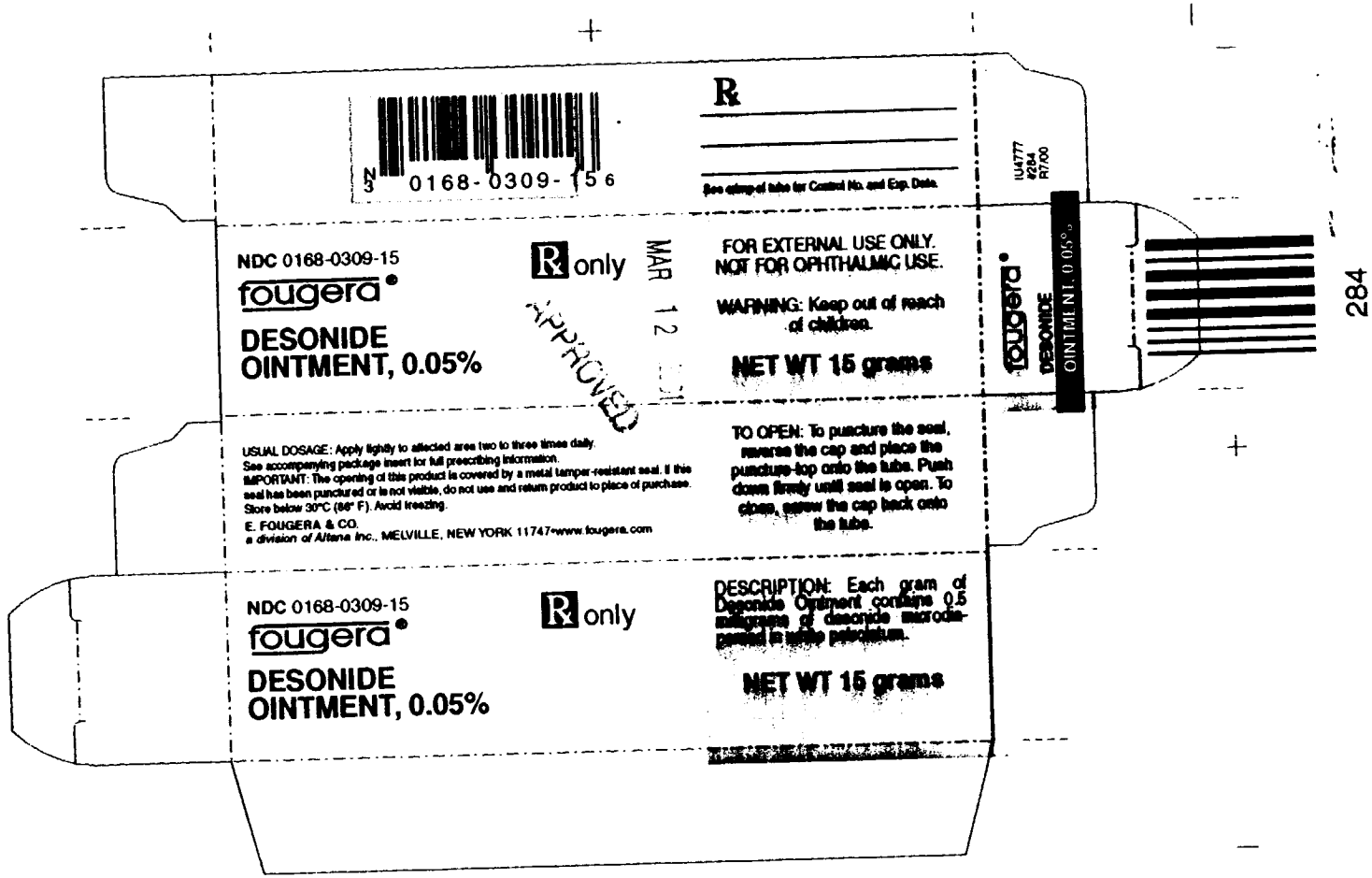
75-751

Labeling Approved

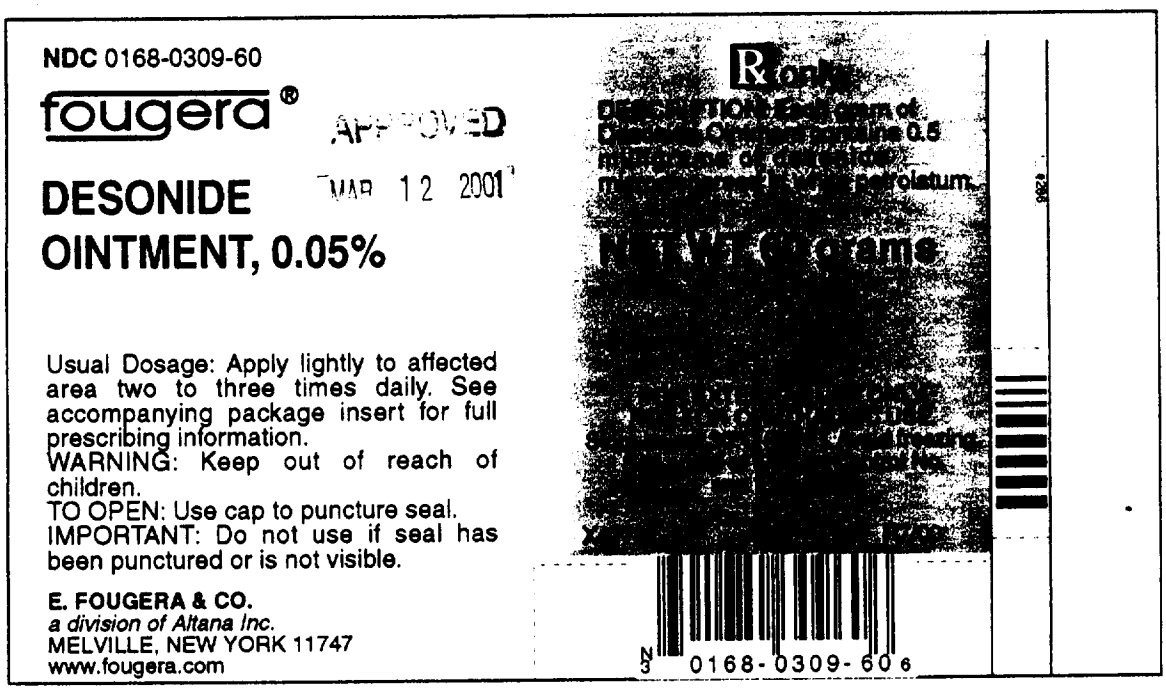
3/12/01



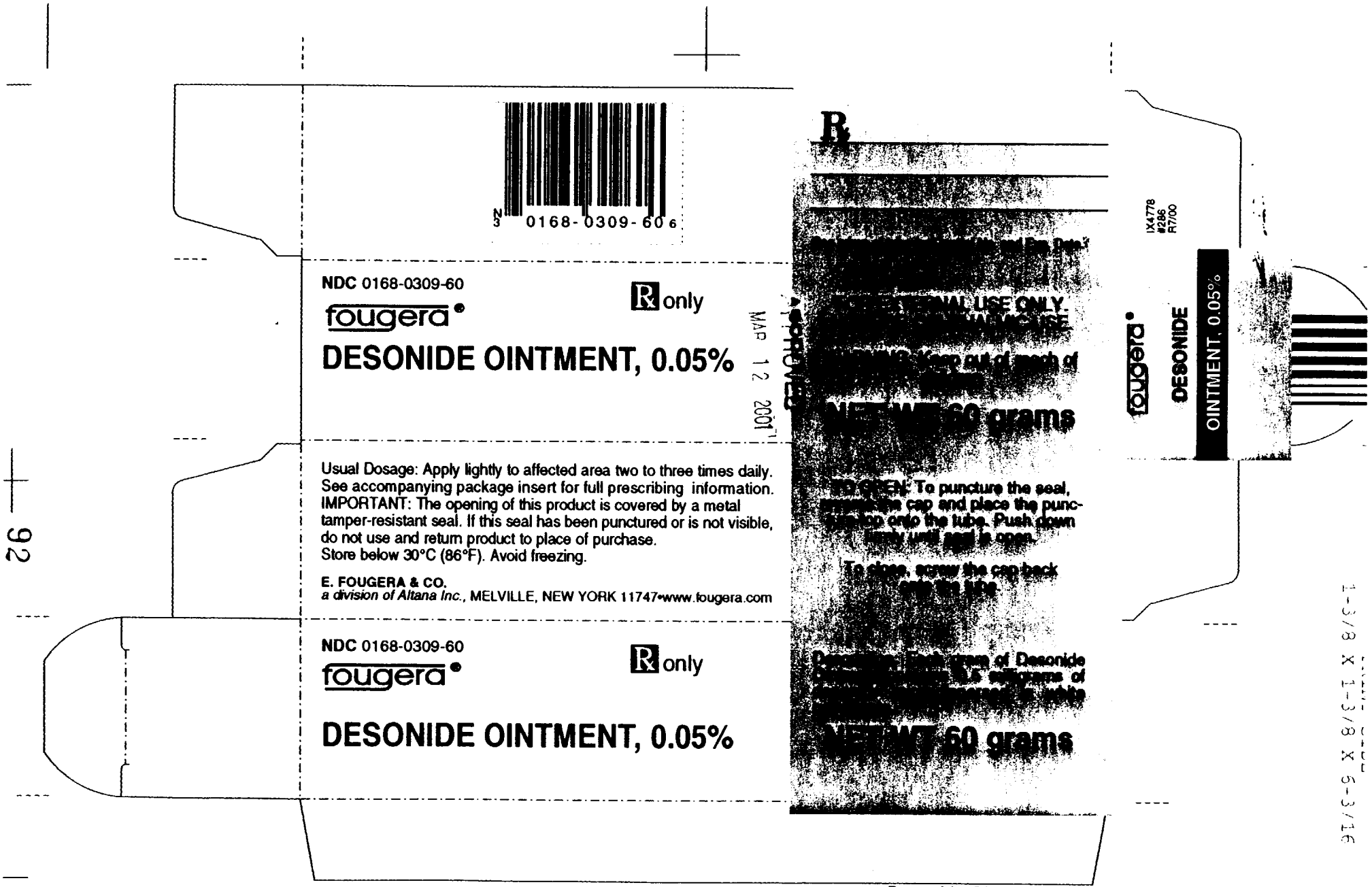
Name: DESONIDE OINTMENT 15g Tube
Die Size: 4 x 3/4 circ 2.281
UPC Code: 0168-0309-15
Pharma Code: #
Colors: PMS Yellow PMS Black



Name: Desonide Ointment 15g Carton
Die Size: 1.063x .875 x 4.250
UPC Code: 0168-0309-15
Pharma Code: #284
Colors: PMS Yellow PMS Black



Desonide Ointment, 0.05% 60 g
Die Size 1 1/8 x 6 circ:3.468
Colors: Black PMS Yellow
Pharma Code: #286



Desonide Ointment60g Cart
Die Size: 1.375 x 1.375 x 6.1875
UPC Code: 0168-0309-60
Pharma Code: #286
Colors: PMS Yellow PMS Black

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-751

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-751

3. NAME AND ADDRESS OF APPLICANT

Altana Inc.
60 Baylis Road
Melville, NY 11747

4. LEGAL BASIS FOR SUBMISSION

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

5. SUPPLEMENT(s)

Original 12/7/99

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Desonide

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

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 6/26/00 - Bio
Amendment 11/1/00

10. PHARMACOLOGICAL CATEGORY

Anti-inflammatory

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's 3939, 9025, 10585, 1627, 7873, 885

13. DOSAGE FORM

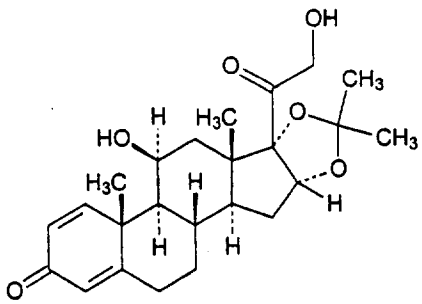
Ointment

14. POTENCY

0.05%

15. CHEMICAL NAME AND STRUCTURE

Desonide. Pregna-1,4-diene-3,20-dione, 11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-, (11β,16α)-.$C_{24}H_{32}O_6$. 416.51. 638-94-8. Anti-inflammatory, glucocortic.



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 2/26/01

Supervisor: Paul Schwartz, Ph.D.

cc: ANDA 75-751
Division File
Field Copy

Endorsement:

HFD-627/NNashed/ NN 3/7/01
HFD-627/PSchwartz/2/26/01 PS 3/7/01

Page(s) 9

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chem Rev 2

2/26/01

JUN 21 2001

38. Chemistry Comments to be Provided to the Applicant.

ANDA: 75-751 APPLICANT: Altana Inc.

DRUG PRODUCT: Desonide Ointment, 0.05%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please revise your drug substance specifications to include a heavy metals test and limits.

2. Please tighten your limits for related substances by TLC and assay value for the drug substance.

3. Please provide the number of samples and where the samples are taken from for your in-process, blend uniformity test.

4. Please explain the reason for having different limits for degradation products and viscosity on p. 1764 from your specifications on p. 1693.

5. Please provide physico-chemical testing on the cap.

6. Please explain "complies with standards specification" for the finished drug product specification.

7. Please explain "degradation 2" on your stability report.

8. Please tighten your stability specifications for the degradation products based on your data.

9. is deficient. The DMF holder has been notified. Please do not respond to this amendment until you have been notified by the DMF holder that the DMF deficiencies have been addressed.

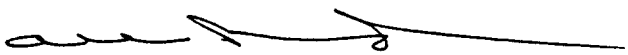
B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The firms referenced in your application regarding the manufacturing and testing the drug product should be in compliance with CGMP at the time of approval.

2. Your bio equivalence study is under review.

3. Your methods validation has been submitted to FDA District Laboratories for validation.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-751

Bioequivalence Review(s)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-751 APPLICANT: Altana Inc.

DRUG PRODUCT: Desonide Ointment, 0.05%

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

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

Sincerely yours,

Barbara M Saint

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

Desonide Ointment
0.05% Ointment
ANDA# 75-751
Reviewer: Pradeep M. Sathe
W# 75751O.600

Altana Inc.
Melville, NY-11747
Submission Dates:
June 26, 2000

Review of Bioequivalence on 0.05% Ointment

Introduction:

Desonide is a non-fluorinated corticosteroid. It is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The mechanism of anti-inflammatory activity of the topical corticosteroid is unclear.

The extent of percutaneous absorption is determined by many factors including the vehicle. Topical steroids can be absorbed from normal skin. Inflammation and other disease processes in the skin increase percutaneous absorption.

History:

The Orange Book lists two other Desonide 0.05% topical ointments besides the innovator Bayer's Desonide^{R} implying that if approved this product will not be considered as the first generic. Following is the approval history of different Desonide topical products:

ANDA#	Firm	Dosage Form	Approval Method
71-425	Galderma	Ointment	Approved based on chemistry. No review from DBE.
72-354	Galderma	Lotion	Approved based on chemistry. No review from DBE.
73-548	Taro	Cream	Approved based on chemistry. No review from DBE.
74027	Copley	Cream	Approved based on chemistry. No review from DBE.
74254	Taro	Ointment	A clinical bio-study (not a skin blanching study) was approved by the medical officer from HFD-540 and statistician in HFD-513

cream as an option.

This therefore is the first ANDA for desonide ointment with a bio-equivalence study with a pharmacodynamic (skin blanching) end point.

Background:

In the applications dated December 7, 1999 and March 29, 2000, the firm provided information on 1. A pilot study performed to establish the ED_{50} value for the dose response curve and 2. A double-blind, randomized trial to demonstrate the equivalency of potency of Tridesilon Ointment to firm's test product desonide ointment 0.05%. The applications were found deficient by the Division and in a review dated June 1, 2000, deficiencies were cited.

Current Amendment:

The amendment consists of firm's response to the cited deficiencies. The deficiencies, firm's response and Division's response are given in that order.

Deficiency 1:

On 3/29/00, you submitted diskette containing the pilot study results. The diskette was accompanied by a hard copy. It was observed that you have used two data points corresponding to 3-hr dose duration for both the left and the right arms. The hard copy, sent with the diskette, also agrees with these sample duration points. The sample scheme seen in the original protocol and original volume 1.5 however does not mention any duplicate 3-hr applications. If the diskette data is to be believed, it is not clear which of the two 3-hr sample data should be used for the calculation of the 30-hr AUEC values (using Chroma-Meter a-scale reading). Please clarify.

Firm's Response:

The confusion indicated in this comment relates to a typographical error in the documentation of the format, for the data in the data diskette. A revised data disk, with accompanying printouts of the contents, has been provided in the format requested by the reviewer. This should clear up any confusion.

Division Response:

Firm's response is acceptable.

Deficiency 2:

Please provide the pilot study data in the correct format. It is strongly recommended that while presenting the data, as far as possible the firm is requested to adhere EXACTLY to the table formats documented in the guidance. Please put the data in three spreadsheets. First Spreadsheet: unadjusted, uncorrected data, Second spreadsheet: Baseline adjusted, uncorrected data, Third spreadsheet: Baseline adjusted, untreated site corrected data. Please use the data using the same column and row formats, as shown in the 'Topical Dermatologic Corticosteroids: In Vivo

Bioequivalence, issued on June 2, 1995' Guidance. E.g. Please put the dose-duration in column and hours after drug removals in row, as seen in Table AIII.1 of the Guidance. When data are corrected for untreated-site readings, please report only the corrected data points in the spreadsheet (e.g. the untreated site readings are reported in the final, baseline-adjusted, untreated-site-corrected results). This will minimize the confusion in the data analysis.

Firm's Response:

Each spreadsheet requested is provided as a worksheet in an Excel file, 9828204.xis. The spreadsheets are in the format suggested by the tables referenced in the June 1995 guidance.

Division Response:

Firm's response is acceptable.

Deficiency 3:

The Guidance recommends inclusion of the responders in the statistical analysis only if D2/D1 ratio is >=1.25. For the calculation of D1 and D2, you have considered any positive AUEC result as zero. Also, while obtaining the D1 or D2 value by averaging the left and right arm AUEC values, you have used these zero values, thereby introducing bias in averaging. This also creates a problem if the overall average from the two arms is negative, (though the individual arm AUEC values are positive and negative respectively).

It appears that, you have included subjects as responders whose $D2/ED_{50}$ ratios are >=1.25 (but whose D2/D1 ratios may not be adequately ascertained). Since the final statistical analysis and confidence intervals are dependent on the subjects included in the analysis, you are requested to clarify how subject # 3, 20, 21, 30, 34, 41, 45, 46, 47, 56, 65, 67, 73 and 74 qualified as responders while subjects # 26, and 28 did not.

Firm's Response:

It is our contention that averaging scores containing negative numbers introduces even more bias than setting them to zero and then averaging. For example subject 41.D2 area scores = 27.61, 20.49 and D1 area scores =-40.37, 2.04. By virtue of being negative, that amount of area due to blanching is cancelled before averaging takes place. This results in avg. (Dl)=-19.17, rather than avg. (D1)=1.02. Thus eliminating a subject who still displays acceptable though minimal blanching response to the D1 test of the reference product.

Previous communications with FDA/OGD staff have indicated that in the case of low potency corticosteroids, the D2/ED50 test may be used as a secondary test if the D2/D1 test fails due to D1 <=O.O. since subjects #26 and #28 had a positive D2/D1 ratio, but <1.25 (i.e. D1>0.0), they did not meet the criteria for the D2/ED50 test, Thus, even though their D2/ED50 ratio was greater than 1.25, they could not be included in the analyses. Altana has submitted many protocols with the same statistical methodology to the OGD and have not been informed that this is unacceptable.

Division Response:

Based on the Guidance, the reviewer calculated the AUEC values, D2/D1 ratios and subsequently the necessary statistics as documented in the Guidance. Based on the D2/D1 ratios, a total of 25 subjects were selected as responders. The statistical evaluation yielded the confidence intervals as between 90.2% to 123.8%.

Deficiency 4:

If possible, please provide the details of how to use MIXNLIN macro.

Firm's Response:

Regarding the use of the SAS macro MIXNLIN, this is proprietary software which accompanies the book, 'Linear and Nonlinear Models for the Analysis of Repeated Measurements", by E. Vonesh & V. Chinchilli, Marcel Dekker, 1997. The appendix to this book contains the complete documentation for installing and running the program, which is probably clearer than can be stated in a short letter. The macro does require the BASE, STAT and IML SAS modules. If the reviewer has these at her disposal, Novum would be able to provide the SAS originally analyze this data.

Division Response:

Firm's response and information has been forwarded to the Division Statistician.

General Comments:

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responders. The reviewer did not

(Attachment II).

Recommendations:

1. The bioequivalence studies conducted by Altana Pharmaceuticals on its 0.05% desonide ointment, lot # C481, comparing it to 0.05% Tridesilon[R] Ointment has been found acceptable by the Division of Bioequivalence. Based on the criterion given in the 'Guidance for Topical Dermatologic Corticosteroids: In-vivo Bioequivalence', the study demonstrates that Altana's 0.05% desonide ointment ~~is~~ may be bioequivalent to the reference product, Bayer's 0.05% Tridesilon[R] Ointment. is

2. From the bioequivalence point of view, the firm has met the requirements of in-vivo bioequivalence and the application is acceptable.

Pradeep M. Sathe, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED BY SGNerurkar
FT INITIALED BY SGNerurkar

12/19/2000

Concur: Barbara M. Davit for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date: 12/22/00

3.1

JUN 19 2000

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-751 APPLICANT: Altana, Inc.

DRUG PRODUCT: Desonide Ointment, 0.05%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

Pilot Study:

1 On 3/29/00, you submitted the diskette containing pilot study results. The diskette was accompanied by a hard copy. It was observed that you have used two data points corresponding to 3-hr dose duration for both the left and the right arms. The hard copy, sent with the diskette, also agrees with these sample duration points. The sample scheme seen in the original protocol and original volume 1.5 however does not mention any duplicate 3-hr applications. If the diskette data is to be believed, it is not clear which of the two 3-hr sample data should be used for the calculation of the 30-hr AUEC values (using Chroma-Meter a-scale reading). Please clarify.

2 Please provide the pilot study data in the correct format. It is strongly recommended that while presenting the data, please adhere EXACTLY to the table format documented in the guidance. Please put the data in three spreadsheets. First Spreadsheet: unadjusted, uncorrected data, Second spreadsheet: Baseline adjusted, uncorrected data, Third spreadsheet: Baseline adjusted, untreated site corrected data. Please use the data using the same column and row formats, as shown in the 'Topical Dermatologic Corticosteroids: In Vivo Bioequivalence, issued on June 2, 1995' Guidance. E.g. Please put the dose-duration in column and hours after drug removals in row, as seen in Table AIII.1 of the Guidance. When data are corrected for untreated-site readings, please report only the corrected data points in the spreadsheet (e.g. the untreated site readings are reported in the final, baseline-adjusted, untreated-site-corrected results). This will minimize the confusion in the data analysis.

Pivotal Study:

3 The Guidance recommends inclusion of the responders in the statistical analysis only if D2/D1 ratio is >=1.25. For the calculation of D1 and D2, you have considered positive AUEC results as zero. Also, while obtaining the D1 or D2 value (by averaging the left and right arm AUEC values), you have used these zero values, thereby introducing bias in averaging. This approach also creates a problem if the overall average from the two arms is negative, (even though the individual arm AUEC values are positive and negative respectively). It appears that, you have included those subjects as responders whose $D2/ED_{50}$ ratios are >=1.25 (but whose D2/D1 ratios may not be adequately ascertained). Since the final statistical analysis and confidence intervals are dependent on the number of subjects included in the analysis, please clarify how subject # 3, 20, 21, 30, 34, 41, 45, 46, 47, 56, 65, 67, 73 and 74 qualified as responders while subjects # 26, and 28 did not.

4 If possible, please provide the details of how to use MIXNLIN macro.

Sincerely yours,

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

Desonide Ointment
0.05% Ointment
ANDA# 75-751
Reviewer: Pradeep M. Sathe
W# 75751S.D99

Altana Inc.
Melville, NY-11747
Submission Dates:
December 7, 1999
March 29, 2000

Review of Bioequivalence on 0.05% Ointment

Background:

Desonide is a non-fluorinated corticosteroid. It is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The mechanism of anti-inflammatory activity of the topical corticosteroid is unclear.

The extent of percutaneous absorption is determined by many factors including the vehicle. Topical steroids can be absorbed from normal skin. Inflammation and other disease processes in the skin increase percutaneous absorption.

The Orange Book lists two other Desonide 0.05% topical ointments besides the innovator Bayer's Desonide^{R} implying that if approved this will not be considered as the first generic product. Following is the approval history of different Desonide topical products:

ANDA#	Firm	Dosage Form	Approval Method
71-425	Galderma	Ointment	Approved based on chemistry. No review from DBE.
72-354	Galderma	Lotion	Approved based on chemistry. No review from DBE.
73-548	Taro	Cream	Approved based on chemistry. No review from DBE.
74027	Copley	Cream	Approved based on chemistry. No review from DBE.
74254	Taro	Ointment	A clinical bio-study (not a skin blanching study) was approved by the medical officer from HFD-540 and statistician in HFD-513

1
to

This therefore is the first ANDA for desonide ointment with a bio-equivalence study with a pharmacodynamic (skin blanching) end point.

Current Application:

The application consists of 1. A pilot study performed to establish the ED_{50} value for the dose response curve and 2. A double-blind, randomized trial to demonstrate the equivalency of potency of Tridesilon Ointment to firm's test product desonide ointment 0.05%.

Drug Product Composition:

INGREDIENTS	TEST mg/g	REFERENCE mg/g
1.Desonide		
2.White Petrolatum, USP		

Pilot Study (Protocol Number

Title: Dose Response of Tridesilon^R Topical Ointment.

Objective: To determine the dose-response relationship for Tridesilon^R topical ointment. The information will be used to estimate ED_{50}, D1 and D2 parameters for use in a full (pivotal) bioequivalence study.

Principal Investigator: Adelaida M. Miro, M.D.

Clinical Facility: Novum Pharmaceutical Research Services,
5900 Penn Avenue,
Pittsburgh, PA 15206

Subjects and Study Design: 15 female subjects studied in one period.

Subject Selection: Screening, Inclusion-Exclusion Criteria; page 1148-1149, volume 1.5

Treatment: Tridesilon^R ointment (Desonide, 0.05%), Bayer Corp.

Dose: A 10 microliter application to the designated sites according to a randomization schedule prepared by Novum Pharmaceutical Research Services prior to dosing.

Methods:

Page(s) 1

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

3/29/00

Safety Evaluations and Precautions:

1. All subjects were screened for alcohol, marijuana and cocaine metabolites using immediate urine testing upon entry into the clinic. Subjects with positive drug screen were not allowed to participate.
2. All subjects had a urine pregnancy test at check-in. Subjects with positive tests were not involved in the study.

Data Analysis:

The post-dose Chroma-Meter and visual readings at each site were corrected for both the average pre-dose reading and average reading for the untreated sites (on the same arm) at the same reading time. The area under the response/time curve for each site was

calculated by the linear trapezoidal method. A population model of the areas under the blanching response, from all subjects, was used to estimate the population dose-response relationship. Nonlinear estimation (Emax model) was used to determine the population ED_{50} and Emax values. The ED_{50} was used to calculate D1 and D2 values, which correspond to approximately one-half and two-times the ED_{50} respectively.

Results:

1. Please see the Deficiencies.

2. Though the presentation of the data from the diskette appears erroneous, the reviewer fitted the firm reported AUEC values from the pilot study using hard copy results submitted in the application dated December 7, 1999. The AUEC values of 15 subjects were fitted using a population simple Emax model as described in the Guidance with 'NONMEM' program. The ED_{50} value obtained in the fitting was around 5.0 hour (Attachment I,a). The same data when fitted using 'Ppharm' program, also gave ED_{50} estimate of around 5 hours [276 mins] (Attachment I,b). The firm reported 'MIXNLIN' estimate of ED_{50} was around 5 hours (Attachment I,c).

Pivotal Study (Protocol Number

Title: Bioequivalence of two topical Desonide 0.05% ointment formulations.

Objective: To compare the relative vasoconstrictor effects of test and reference topical desonide 0.05% ointments in asymptomatic subjects.

Principal Investigator: Adelaida M. Miro, M.D.

Clinical Facility: Novum Pharmaceutical Research Services,
5900 Penn Avenue,
Pittsburgh, PA 15206

Subjects and Study Design: Seventy-four (74) pre-screened, asymptomatic, healthy, non-tobacco using, female subjects were selected (age range: 18-49 years, within 20% of the ideal weight) for the study. Seventy-two (72) subjects completed the study. Subject numbers 5 and 63 withdrew from the study participation for nausea and for personal reasons respectively and were not included in the data report. The firm claims that a total of 37 of the 72 subjects met the qualifying (D2/D1>=1.25) criteria for the Chroma-Meter study (please see comments). The study design was a one period, randomized, two treatment. The firm ascertained ED_{50}, D1 and D2 values (based on the pilot study AUEC values of 15 subjects) were 5 hours, 2.5 hours and 10 hours, respectively.

Subject Selection Criteria: Screening, Inclusion-Exclusion Criteria; page 142-144, volume 1.2.

Treatments:

Reference: Tridesilon^{R} ointment (Desonide, 0.05%), Bayer Corp., Lot 8EER, expiration 05/01, applied for a dose duration of 5 hours.
Test: Desonide 0.05% ointment, Altana Inc., Lot C481, Manufacture Date: 10/98, applied for a dose duration of 5 hours.
D1: Tridesilon^{R} ointment (Desonide, 0.05%), Bayer Corp., Lot 8EER, expiration 05/01, applied for a dose duration of 2.5 hours.
D2: Tridesilon^{R} ointment (Desonide, 0.05%), Bayer Corp., Lot 8EER, expiration 05/01, applied for a dose duration of 10 hours.

The test and reference treatments corresponding to ED_{50} were applied to each arm as a replicate i.e. T1, T2 or R1, R2

Methods:

Randomization: The ointments were applied to 6 sites on the flexor surface of each forearm. Two sites were untreated evaluation sites.

1. Procedure: Eight (8) sites were designated on the flexor surface of each forearm, between wrist and elbow. A 10µl dose was applied to 6 of the randomly determined sites according to the following a staggered application, synchronized removal scheme. Two sites on each arm were left untreated.

Day	Clock Time	Hour	Event
1	0300-0500		Baseline assessments, all sites
	0500	-10.00	Apply 10 hour duration-Reference (D2)
	1000	-5.00	Apply 5 hour duration-Reference, Test (ED_{50})
	1330	-2.5	Apply 2.5 hour duration-Reference (D1)
	1500	0.00	Remove ointments from all sites on both arms; wipe untreated sites in a similar manner. Visual and Chroma-Meter assessments
	1700	2.00	Visual and Chroma-Meter assessments
	1900	4.00	Visual and Chroma-Meter assessments
	2100	6.00	Visual and Chroma-Meter assessments
	2300	8.00	Visual and Chroma-Meter assessments
2	0100	10.00	Visual and Chroma-Meter assessments.
	0300	12.00	Visual and Chroma-Meter assessments.
	1100	20.00	Visual and Chroma-Meter assessments.
	1500	24.00	Visual and Chroma-Meter assessments.
	2100	30.00	Visual and Chroma-Meter assessments.

2. Preparation: The arms of each subject were washed with a mild soap and gently dried within approximately 2 hours prior to the initial dosing.

3. Sites: An open washer (inside diameter of approximately 1.6 cm) was placed over each of the 10 sites and taped in place on its edges with hypo-allergic tape. Sites were not within 3 cm of the wrist or ante-cubital fossa, nor were washers closer than 2 cm apart center to center. All sites were numbered for ease of identification; sites 1-8 on the right arm and sites 9-16 on the left arm.

4. Application (Staggered): The ointment was applied within the application sites using a 250µl glass Hamilton syringe. It was evenly spread within the site using the conical tip of a tube. All sites remained non-occluded throughout the study. The ointment was applied to sites at staggered application times of 10 hours, 5 hours and 2.5 hours prior to simultaneous removal at time 0 (0.0 hour).

5. Removal (Synchronized): All applications were removed at the same time (Time 0) with the shortest duration removed first. All treated sites were gently wiped at least 3 times with a separate cotton ball to remove the treatment. The untreated sites were similarly wiped at the same time as the treated sites.

6. Assessments: All sites were assessed under standard lighting and at room temperature prior to application, and at 0, 2, 4, 6, 8, 10, 12, 20, 24 and 30 hours after product removal. The evaluator and the Chroma-Meter operator did not have knowledge of the duration of the treatment at each site.

Visual: The degree of skin blanching was visually evaluated for each site by a trained evaluator according to the following rating scale:

0= No pallor, no change from surrounding area
1=Mild pallor, slight or indistinct outline of application site
2=Moderate pallor, discernible outline of application site
3=Intense pallor, clean, distinct outline of application site

Chroma-Meter: Assessments were made electronically using the Chroma-Meter a-scale. Duplicate readings were performed on each site at the pre-dose assessment time.

7. Confinement: Subjects entered the clinical facility on Day –1 by 2000 hours and remained confined until at least 38 hours after the first application (dosing).

8. Meals: Meals were served at traditional meal times, no caffeine or alcohol was permitted during the study. Water was permitted ad-lib throughout the study.

9. Restrictions: Subjects were asked not to wear anything that would leave a mark or otherwise change the color of the arm, such as tight clothing or watch. They were asked not to rest their heads on their arms during the hour prior to an assessment. Subjects were

instructed to avoid water on their arms, extremes of temperature and physical exercise during the study.

Validation:

The firm has provided Chroma-Meter a-scale validation information using 4 subjects on separate days with 3 evaluators. The information is given in Attachment II. The information indicates that the within or between site CV was less than 7.5%, indicating adequate precision of the readings.

Results:

The firm's calculated Statistics using N=37, is given in Attachment III. Attachment IV gives the mean profiles of different treatments (as reported by the firm). Please see the 'Deficiencies'.

General Comments:

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Deficiencies:

Pilot Study:

1. On 3/29/00, the firm submitted the diskette containing the pilot study results. The diskette was accompanied by a hard copy. It was observed that the firm has used two data points corresponding to 3-hr dose duration for both the left and the right arms. The hard copy, sent with the diskette, also agrees with these sample duration points. The sample scheme seen in the original protocol and original volume 1.5 however does not mention any duplicate 3-hr applications. If the diskette data is to be believed, it is not clear which of the two 3-hr sample data should be used for the calculation of the 30-hr AUEC values (using Chroma-Meter a-scale reading). Please clarify.

2. Please provide the pilot study data in the correct format. It is strongly recommended that while presenting the data, please adhere **EXACTLY** to the table format documented in the guidance. Please put the data in three spreadsheets. First Spreadsheet: unadjusted, uncorrected data, Second spreadsheet: Baseline adjusted, uncorrected data, Third spreadsheet: Baseline adjusted, untreated site corrected data. **Please use the data using the same column and row formats, as shown in the 'Topical Dermatologic Corticosteroids: In Vivo Bioequivalence, issued on June 2, 1995' Guidance.** E.g. Please put the dose-duration in column and hours after drug removals in row, as seen in Table AIII.1 of the Guidance. When data are corrected for untreated-site readings, please report only the corrected data points in the spreadsheet (e.g. the untreated site readings are reported in the final, baseline-adjusted, untreated-site-corrected results). This will minimize the confusion in the data analysis.

Pivotal Study:

3. The Guidance recommends inclusion of the responders in the statistical analysis only if D2/D1 ratio is >=1.25. For the calculation of D1 and D2, the firm has considered

any positive AUEC result as zero. Also, while obtaining the D1 or D2 value by averaging the left and right arm AUEC values, the firm has used these zero values, thereby introducing bias in averaging. This also creates a problem if the overall average from the two arms is negative, (though the individual arm AUEC values are positive and negative respectively). It appears that, the firm has included subjects as responders whose $D2/ED_{50}$ ratios are >=1.25 (but whose D2/D1 ratios may not be adequately ascertained). Since the final statistical analysis and confidence intervals are dependent on the subjects included in the analysis, the firm is requested to clarify how subject # 3, 20, 21, 30, 34, 41, 45, 46, 47, 56, 65, 67, 73 and 74 qualified as responders while subjects # 26, and 28 did not.

4. If possible, please provide the details of how to use MIXNLIN macro.

Recommendations:

1. The bioequivalence studies conducted by Altana Pharmaceutical on its 0.05% desonide ointment, lot # C481, comparing it to 0.05% Tridesilon Ointment has been found incomplete by the Division of Bioequivalence at this time. Due to data documentation error and confusing presentation of the data diskette, accurate estimation of the ED_{50} value was not possible for the pilot study. Consequently, the pivotal study data analysis also cannot be considered definitive at this time.

2. Deficiencies 1-4 should be forwarded to the firm.

Sathe 5/26/00
Pradeep M. Sathe
Review Branch II
Division of Bioequivalence

RD INITIALED BY SGNerurkar
FT INITIALED BY SGNerurkar 5/26/2000

Concur: _____ Date: 6/1/2000
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

DIVISION FILE:

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-751 APPLICANT: Altana, Inc.

DRUG PRODUCT: Desonide Ointment, 0.05%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

Pilot Study:

1 On 3/29/00, you submitted the diskette containing pilot study results. The diskette was accompanied by a hard copy. It was observed that you have used two data points corresponding to 3-hr dose duration for both the left and the right arms. The hard copy, sent with the diskette, also agrees with these sample duration points. The sample scheme seen in the original protocol and original volume 1.5 however does not mention any duplicate 3-hr applications. If the diskette data is to be believed, it is not clear which of the two 3-hr sample data should be used for the calculation of the 30-hr AUEC values (using Chroma-Meter a-scale reading). Please clarify.

2 Please provide the pilot study data in the correct format. It is strongly recommended that while presenting the data, please adhere EXACTLY to the table format documented in the guidance. Please put the data in three spreadsheets. First Spreadsheet: unadjusted, uncorrected data, Second spreadsheet: Baseline adjusted, uncorrected data, Third spreadsheet: Baseline adjusted, untreated site corrected data. Please use the data using the same column and row formats, as shown in the 'Topical Dermatologic Corticosteroids: In Vivo Bioequivalence, issued on June 2, 1995' Guidance. E.g. Please put the dose-duration in column and hours after drug removals in row, as seen in Table AIII.1 of the Guidance. When data are corrected for untreated-site readings, please report only the corrected data points in the spreadsheet (e.g. the untreated site readings are reported in the final, baseline-adjusted, untreated-site-corrected results). This will minimize the confusion in the data analysis.

Pivotal Study:

3 The Guidance recommends inclusion of the responders in the statistical analysis only if D2/D1 ratio is >=1.25. For the calculation of D1 and D2, you have considered positive AUEC results as zero. Also, while obtaining the D1 or D2 value (by averaging the left and right arm AUEC values), you have used these zero values, thereby introducing bias in averaging. This approach also creates a problem if the overall average from the two arms is negative, (even though the individual arm AUEC values are positive and negative respectively). It appears that, you have included those subjects as responders whose $D2/ED_{50}$ ratios are >=1.25 (but whose D2/D1 ratios may not be adequately ascertained). Since the final statistical analysis and confidence intervals are dependent on the number of subjects included in the analysis, please clarify how subject # 3, 20, 21, 30, 34, 41, 45, 46, 47, 56, 65, 67, 73 and 74 qualified as responders while subjects # 26, and 28 did not.

4 If possible, please provide the details of how to use MIXNLIN macro.

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-751

ADMINISTRATIVE DOCUMENTS

APPROVAL PAKAGE SUMMARY FOR 75-751

ANDA:75-751

FIRM: Altana Inc.

DRUG: Desonide

DOSAGE: Ointment

STRENGTH: 0.05%

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 2/8/00.

BIO STUDY/BIOEQUIVALENCE STATUS: Bio is satisfactory 12/22/00

METHODS VALIDATION: Pending

STABILITY: The firm has submitted satisfactory 3 months accelerated stability data at 40°C/75%RH, 18 months room temperature at 25°C/60%RH and cycling study for both packaging sizes. The stability samples stored on side.

LABELING: labeling is satisfactory 11/27/00

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has provided master formula and manufacturing instructions for intended production batch g. The firm has submitted a copy of the executed batch lot #C481 for The firm will use the same drug substance manufacturer, same manufacturing process, and same equipment.

COMMEMTS: The application is approvable - Pending method validation.

Reviewer: Nashed E. Nashed, Ph.D. Date: 2/26/01

Supervisor: Paul Schwartz, Ph.D. p/ 2/26/01

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

ANDA Number: 75-751 Date of Submission: December 7, 1999

Applicant's Name: Altana, Inc.

Established Name: Desonide Ointment, 0.05%

Labeling Deficiencies:

1. CONTAINER (15 g and 60 g) – Satisfactory in draft

2. CARTON (15 g and 60 g) – Satisfactory in draft

3. INSERT (DOSAGE AND ADMINISTRATION)

   Revise the dosing interval to read, ...two to three times... rather than two to four times... to provide consistency throughout your labeling.

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

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-751

CORRESPONDENCE

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

NDA ORIG AMENDMENT
N/Ans

February 28, 2001

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

ANDA 75-751 Desonide Ointment 0.05%

Telephone Amendment

Dear Dr. Patel:

Reference is made to the Altana Inc. Abbreviated New Drug Application for Desonide Ointment, 0.05% submitted December 7, 1999 pursuant to Section 505 (j) of the Federal Food Drug and Cosmetic Act, as well as to the Agency's correspondence dated June 21, 2000 and Altana Inc.'s response of November 1, 2000.

Reference is also made to a telephone request of February 28, 2001 wherein Altana Inc. was requested to provide a commitment to assist the FDA laboratory in validating the analytical methodology.

As requested a commitment to assist the laboratory is included.

Please contact me at (631) 454-7677 extension 2091, if you require any additional information or clarification. Fax communications may be made to (631) 756-5114.

Sincerely,

ALTANA INC.

Virginia Carman

Virginia Carman
Associate Director, Regulatory Affairs

Enclosure

VC/cc

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

November 1, 2000

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Via Federal Express

NDA ORIG AMENDMENT
N/Am

ANDA 75-751
Desonide Ointment, 0.05%
MINOR AMENDMENT

Dear Mr. Rickman:

Reference is made to the Altana Inc. Abbreviated New Drug Application for Desonide Ointment, 0.05% submitted December 7, 1999, pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Altana Inc. acknowledges receipt of the following FDA correspondence dated June 21, 2000. As requested this response has been appropriately identified as a MINOR AMENDMENT.

Each item has been addressed in **comment**/response format.

CHEMISTRY DEFICIENCIES:

1. **Please revise your drug substance specifications to include a heavy metals test and limits.**

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

11/1/00

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Altana Inc. acknowledges that the methods validation has been submitted to the FDA District Laboratories for validation.

LABELING DEFICIENCIES:

1. **CONTAINER (15 g AND 60 g) - Satisfactory in draft.**

2. **CARTON (15 g and 60 g) - Satisfactory in draft.**

3. **INSERT (DOSAGE AND ADMINISTRATION)**

Revise the dosing interval to read, ...two to three times... rather than two to four times...to provide consistency throughout your labeling.

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

The insert labeling has been revised to state "...two to three times..." as instructed. Final printed labeling for the container, carton and insert have been included as Attachment IX.

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.

A side-by-side comparison for each labeling piece (container, carton and package insert) has been included as Attachment X.

Attachment XI contains a revised Post-Approval Stability Commitment and Protocol.

This concludes Altana's response to this Minor Amendment. If you have any questions or require additional clarification please contact me at (631) 454-7677 extension 2091. Fax communications may be made to (631) 756-5114.

Sincerely
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director, Regulatory Affairs

VC:ab

Enclosures

C:\Amendments\Desonide Ointment, 0.05%\Deficiency letter of 6-21-00.wpd

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

June 26, 2000

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

VIA FEDERAL EXPRESS

ORIG AMENDMENT
N/A B

ANDA 75-751
Desonide Ointment, 0.05%
BIOEQUIVALENCY AMENDMENT

Dear Mr. Conner:

Reference is made to the Altana Inc. original Abbreviated New Drug Application for Desonide Ointment, 0.05% submitted on December 7, 1999, pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act. Reference is also made to Altana's March 29, 2000 Amendment, in which the bioequivalency data was submitted on diskette.

Reference is also made to the FDA correspondence of June 9, 2000 which included several comments regarding the bioequivalence study submitted in the original application.

Altana Inc. has prepared the enclosed correspondence to address the FDA comments with the assistance of Novum Pharmaceutical Research Services, the CRO responsible for conducting the bioequivalence study.

Each item has been addressed in **comment**/response format.

Pilot Study

1. **On 3/29/00, you submitted the diskette containing pilot study results. The diskette was accompanied by a hard copy. It was observed that you have used two data points corresponding to 3-hr dose duration for both the left and the right arms. The hard copy, sent with the diskette, also agrees with these sample duration points. The sample scheme seen in the original protocol and original volume 1.5, however does not mention any duplicated 3-hr applications. If the diskette data is to be believed, it is not clear which of the two 3-hr sample data should be used for the calculation of the 3-hr AUEC values (using Chroma-Meter a-scale reading). Please clarify.**

The confusion indicated in this comment relates to a typographical error in the documentation of the format, for the data in the data diskette. A revised data disk, with accompanying printouts of the contents, has been provided in the format requested by the reviewer. This should clear up any confusion.

2. **Please provide the pilot study data in the correct format. It is strongly recommended that while presenting the data, please adhere EXACTLY to the table format documented in the guidance. Please put the data in three spreadsheets. First Spreadsheet: unadjusted, uncorrected data, Second spreadsheet: Baseline adjusted, uncorrected data, Third spreadsheet: Baseline adjusted, untreated site corrected data. Please use the data using the same column and row formats, as shown in the 'Topical Dermatologic Corticosteroids: In Vivo Bioequivalence, issued on June 2, 1995' Guidance. E.g. Please put the dose-duration in column and hours after drug removals in row, as seen in Table AIII.1 of the Guidance. When data are corrected for untreated-site readings, please report only the corrected data points in the spreadsheet (e.g. the untreated site readings are reported in the final, baseline-adjusted, untreated-site-corrected results). This will minimize the confusion in the data analysis.**

Each spreadsheet requested is provided as a worksheet in an Excel file, 9828204.xls. The spreadsheets are in the format suggested by the tables referenced in the June 1995 guidance.

Pivotal Study

3. **The Guidance recommends inclusion of the responders in the statistical analysis only if D2/D1 ration is >=1.25. For the calculation of D1 and D2, you have considered positive AUEC results as zero. Also, while obtaining the D1 or D2 value (by averaging the left and right arm AUEC values), you have used these zero values, thereby introducing bias in averaging. This approach also creates a problem if the overall average from the two arms is negative, (even though the individual arm AUEC values are positive and negative respectively).**

It is our contention that averaging scores containing negative numbers introduces even more bias than setting them to zero and then averaging. For example subject 41.D2 area scores = 27.61, 20.49 and D1 area scores =-40.37, 2.04. By virtue of being negative, that amount of area due to blanching is cancelled before averaging takes place. This results in avg. (D1)=-19.17, rather than avg. (D1)=1.02. Thus eliminating a subject who still displays acceptable though minimal blanching response to the D1 test of the reference product.

It appears that, you have included those subjects as responders whose D2/ED50 rations are >=1.25 (but whose D2/D1 ratios may not be adequately ascertained). Since the final statistical analysis and confidence intervals are dependent on the number of subjects included in the analysis, please clarify how subject #3, 20, 21, 30, 34, 41, 45, 46, 47, 56, 65, 67, 73 and 74 qualified as responders while subjects #26, and 28 did not.

Previous communications with FDA/OGD staff have indicated that in the case of low potency corticosteroids, the D2/ED50 test may be used as a secondary test if the D2/D1 test fails due to D1 <=0.0. since subjects #26 and #28 had a positive D2/D1 ratio, but <1.25 (i.e. D1>0.0), they did not meet the criteria for the D2/ED50 test. Thus, even though their D2/ED50 ration was greater than 1.25, they could not be included in the analyses. Altana has submitted many protocols with the same statistical methodology to the OGD and have not been informed that this is unacceptable.

4. **If possible, please provide the details of how to use MIXNLIN macro.**

Regarding the use of the SAS macro MIXNLIN, this is proprietary software which accompanies the book, 'Linear and Nonlinear Models for the Analysis of Repeated Measurements", by E. Vonesh & V. Chinchilli, Marcel Dekker, 1997. The appendix to this book contains the compete documentation for installing and running the program, which is probably clearer than can be stated in a short letter. The macro does require the BASE, STAT and IML SAS modules. If the reviewer has these at her disposal, Novum would be able to provide the SAS script used to originally analyze this data.

If further clarification or assistance is needed, please contact me at (631) 454-7677 extension 2091. If necessary, a telecon can be arranged with Novum Pharmaceutical Research Services. Fax communications may be made to (631) 756-5114.

Sincerely,
Altana Inc.

Jacqueline Bazzetta For/
Virginia Carman
Associate Director, Regulatory Affairs

VC/et

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

March 29, 2000

AB

NDA 075-751 AMENDMENT

Ms. Jennifer Fan
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 286
7500 Standish Place
Rockville, Maryland 20855-2773

VIA FEDERAL EXPRESS

Re: ANDA 75-751 Bioequivalence Amendment
Desonide Ointment, 0.05%

Dear Ms. Fan:

As per a request from the Division to submit from the pilot bioequivalence study on diskette, please find enclosed two diskettes containing the pilot study, as well as a hard copy of the data. Please forward this information to Mr. Sathe.

Thank you for your assistance.

If any further information is required, please contact me at (631) 454-7677, extension 2091.

Please note our new fax number is (631) 756-5114.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director, Regulatory Affairs

Enclosures
VC/et

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 631-454-7677

Federal Express

February 1, 2000

75-751

NEW CORRESP
NC

Paras Patel
Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 286
7500 Standish Place
Rockville, Maryland 20855-2773

Re: ANDA: New Submission Telephone Amendment
Desonide Ointment, 0.05%

Dear Mr. Patel:

Reference is made to our original Abbreviated New Drug Application submitted December 7, 1999 and our amendment of January 12, 2000.

Reference is further made to our telephone conversation of January 24, 2000 requesting the labeling comparison, which was inadvertently omitted from our January 12th amendment.

As requested, please find enclosed a side by side comparison of our labeling is the innovator labeling.

Also included is a data diskette containing information on our bioequivalence study. This is included in the review copy.

If any further information is required, please do not hesitate to contact me at (631) 454-7677, extension 2091.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

Enclosures

VC/et

MW 2-4-00

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ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-756-5114 BYK GULDEN PHARMA GROUP

Federal Express

January 12, 2000

NEW CORRESP
NC.

Paras Patel
Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 286
7500 Standish Place
Rockville, Maryland 20855-2773

Re: ANDA: New Submission Telephone Amendment
Desonide Ointment, 0.05% 75-751

Dear Mr. Patel:

Reference is made to our original Abbreviated New Drug Application submitted December 7, 1999.

Reference is further made to our telephone conversation of January 6, 2000 requesting several revisions to our original application due to a change in the ownership of the reference-listed drug.

As requested, please find enclosed a revised cover letter, 356H, Basis for ANDA Submission, Patent and Exclusivity Certifications and Labeling Certifications.

Also included is a data diskette containing information on our bioequivalence study. This is included in the review copy.

If any further information is required, please do not hesitate to contact me at (631) 454-7677, extension 2091.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

Enclosures

VC/et

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 13 2000
OGD

N 21-751

ALTANA

Altana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-756-5114 BYK GULDEN PHARMA GROUP

Federal Express

January 12, 2000

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

Re: Original Submission
Abbreviated New Drug Application
Desonide Ointment, 0.05%

Dear Sir or Madam:

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

The reference listed drug that is the basis for this submission is Tridesilon Topical Ointment 0.05% (desonide ointment) (NDA 17-426), manufactured by Clay Park. The proposed drug, Desonide Ointment, 0.05%, contains the same active ingredient in the same strength and dosage form, has the same indications and usage, and route of administration as the reference listed drug.

The exhibit batch (#C481) included in this application was fully packaged utilizing the 15 gram and 60 gram presentations for which approval is currently requested. The number of units filled of each package size and the disposition of any remaining bulk product are reconciled in the exhibit batch record.

Included in this eight (8) volume submission, along with Form FDA 356h, is the required Patent Certification and Exclusivity statements, draft Labeling, Bioequivalence , full Components and Composition statements, Raw Materials controls, description of the Manufacturing Facilities, Manufacturing and Processing instructions, In-process Controls,

NDA 22-426

Filling and Packaging procedures, information on the Container/Closure System, controls for the Finished Dosage Form, Analytical Methods, Finished Dosage Form Stability, Environmental Impact Analysis statement and Certification Requirements of the Generic Drug Enforcement Act of 1992.

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

Virginia Carman
Associate Director
Regulatory Affairs
Altana Inc.
60 Baylis Road
Melville, NY 11747
Tel. No. (516) 454-7677 Ext. 2091
Fax No. (516) 756-5114

A certified copy of this application consisting of volumes, 1.1, 1.6, 1.7 and 1.8 and a copy of the Methods Validation package is being sent to the New York District Office under separate cover.

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

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

Enclosures

VC/ab

C:\ANDAS\Desonide Oint. 0.05%\cover letter.wpd

ANDA 75-751

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

FEB 2 2000

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 the telephone conversation dated January 6, 2000 and to your correspondence dated January 12, 2000.

NAME OF DRUG: Desonide Ointment, 0.05%

DATE OF APPLICATION: December 7, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 13, 1999

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:

Elaine Hu
Project Manager
(301) 827-5848

Sincerely yours,

for

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ALTANA

ana Inc. 60 Baylis Road, Melville, N.Y. 11747 516-454-7677 Fax: 516-756-5114 BYK GULDEN PHARMA GROUP

Federal Express

December 7, 1999

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

Re: Original Submission
Abbreviated New Drug Application
Desonide Ointment, 0.05%

Dear Sir or Madam:

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

The reference listed drug that is the basis for this submission is Tridesilon® 0.05% (desonide ointment) (NDA 17-426), manufactured by Bayer Corporation. The proposed drug, Desonide Ointment, 0.05%, contains the same active ingredient in the same strength and dosage form, has the same indications and usage, and route of administration as the reference listed drug.

The exhibit batch (#C481) included in this application was fully packaged utilizing the 15 gram and 60 gram presentations for which approval is currently requested. The number of units filled of each package size and the disposition of any remaining bulk product are reconciled in the exhibit batch record.

Included in this eight (8) volume submission, along with Form FDA 356h, is the required Patent Certification and Exclusivity statements, draft Labeling, Bioequivalence , full Components and Composition statements, Raw Materials controls, description of the Manufacturing Facilities, Manufacturing and Processing instructions, In-process Controls,

Filling and Packaging procedures, information on the Container/Closure System, controls for the Finished Dosage Form, Analytical Methods, Finished Dosage Form Stability, Environmental Impact Analysis statement and Certification Requirements of the Generic Drug Enforcement Act of 1992.

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

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Associate Director
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60 Baylis Road
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Tel. No. (516) 454-7677 Ext. 2091
Fax No. (516) 756-5114

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

Sincerely,
Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

Enclosures

VC/ab

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