CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-373

APPROVAL LETTER

ANDA 75-373

JUN 22 1999

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

Dear Madam:

This is in reference to your abbreviated new drug application dated May 1, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Betamethasone Dipropionate Ointment USP (Augmented), 0.05% (base).

Reference is also made to your amendments dated August 18 and August 25, 1998; and January 29, March 31, and May 26, 1999.

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 Betamethasone Dipropionate Ointment USP (Augmented), 0.05% (base) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Diprolene® Ointment, 0.05% (base) of Schering Corporation).

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 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.

Sincerely yours,

D. L. Sporn 6/22/99

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

cc:

Endorsements:

6/11/99

6/11/99
1999

Rec'd 6/14/99

Robert Lumpkin
6/22/99

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-373

APPROVED DRAFT LABELING

fougera®

BETAMETHASONE DIPROPIONATE OINTMENT USP (AUGMENTED*), 0.05%

(Potency expressed as betamethasone)

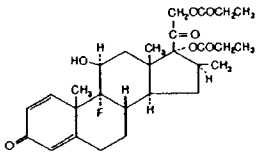
*** Vehicle augments the penetration of the steroid.**

FOR DERMATOLOGICAL USE ONLY **NOT FOR OPHTHALMIC USE**

℞ only

DESCRIPTION: Betamethasone dipropionate ointment (augmented) contains betamethasone dipropionate, USP, a synthetic adrenocorticosteroid, for dermatologic use. Betamethasone, an analog of prednisolone, has a high degree of corticosteroid activity and a slight degree of mineralocorticoid activity. Betamethasone dipropionate is the 17,21-dipropionate ester of betamethasone.

Chemically, betamethasone dipropionate is 9-fluoro-11β,17,21-trihydroxy-16β-methyl-pregna-1,4-diene-3,20-dione 17,21-dipropionate, with the molecular formula $C_{28}H_{37}FO_7$, a molecular weight of 504.6, and the following structural formula:



Betamethasone dipropionate is a white to creamy white, odorless crystalline powder, insoluble in water. Each gram of betamethasone dipropionate ointment (augmented) contains: 0.64 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in an augmented vehicle of propylene glycol, propylene glycol stearate, white wax and white petrolatum.

CLINICAL PHARMACOLOGY: The corticosteroids are a class of compounds comprising steroid hormones secreted by the adrenal cortex and their synthetic analogs. In pharmacologic doses, corticosteroids are used primarily for their anti-inflammatory and/or immunosuppressive effects.

Topical corticosteroids, such as betamethasone dipropionate, are effective in the treatment of corticosteroid-responsive dermatoses primarily because of their anti-inflammatory, anti-pruritic, and vasoconstrictive actions. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well known, the exact mechanisms of their actions in each disease are uncertain. Betamethasone dipropionate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

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. (See **DOSAGE AND ADMINISTRATION** section.)

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. (See **DOSAGE AND ADMINISTRATION** section.)

Once absorbed through the skin, topical corticosteroids enter 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.

At 14 g per day, betamethasone dipropionate ointment (augmented) was shown to depress the plasma levels of adrenal cortical hormones following repeated application to diseased skin in patients with psoriasis. Adrenal depression in these patients was transient, and rapidly returned to normal upon cessation of treatment. At 7 g per day (3.5 g bid), betamethasone dipropionate ointment (augmented) was shown to cause minimal inhibition of the hypothalamic-pituitary-adrenal (HPA) axis when applied two times daily for 2 to 3 weeks, in normal patients and in patients with psoriasis and eczematous disorders.

With 6 to 7 g of betamethasone dipropionate ointment (augmented) applied once daily for 3 weeks, no significant inhibition of the HPA axis was observed in patients with psoriasis and atopic dermatitis, as measured by plasma cortisol and 24-hour urinary 17-hydroxy-corticosteroid levels.

INDICATIONS AND USAGE: Betamethasone dipropionate ointment (augmented), is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS: Betamethasone dipropionate ointment (augmented), is contraindicated in patients who are hypersensitive to betamethasone dipropionate, to other corticosteroids, or to any ingredient in this preparation.

PRECAUTIONS: General: Systemic absorption of topical corticosteroids has produced reversible 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 corticosteroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. (See **DOSAGE AND ADMINISTRATION** section.)

(over)

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area 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 imitation 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.

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

1. This medication is to be used as directed by the physician and should not be used longer than the prescribed time period. 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 that for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive. (See **DOSAGE AND ADMINISTRATION** section.)
4. Patients should report any signs of local adverse reactions.

Laboratory Tests: The following tests may be helpful in evaluating 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 topically applied corticosteroids.

Studies to determine mutagenicity with prednisolone 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 of the teratogenic effects of topically applied corticosteroids in pregnant women. 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 prescribed for a nursing woman.

Pediatric Use: Use of betamethasone dipropionate ointment (augmented) in pediatric patients under 12 years is not recommended.

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 when topical corticosteroids are used as recommended. 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.

The following adverse reactions have also been reported with betamethasone dipropionate ointment (augmented): erythema and vesiculation.

Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

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

DOSAGE AND ADMINISTRATION: Apply a thin film of betamethasone dipropionate ointment (augmented) to the affected skin areas once or twice daily. Treatment with betamethasone dipropionate ointment (augmented) should be limited to 45 g per week.

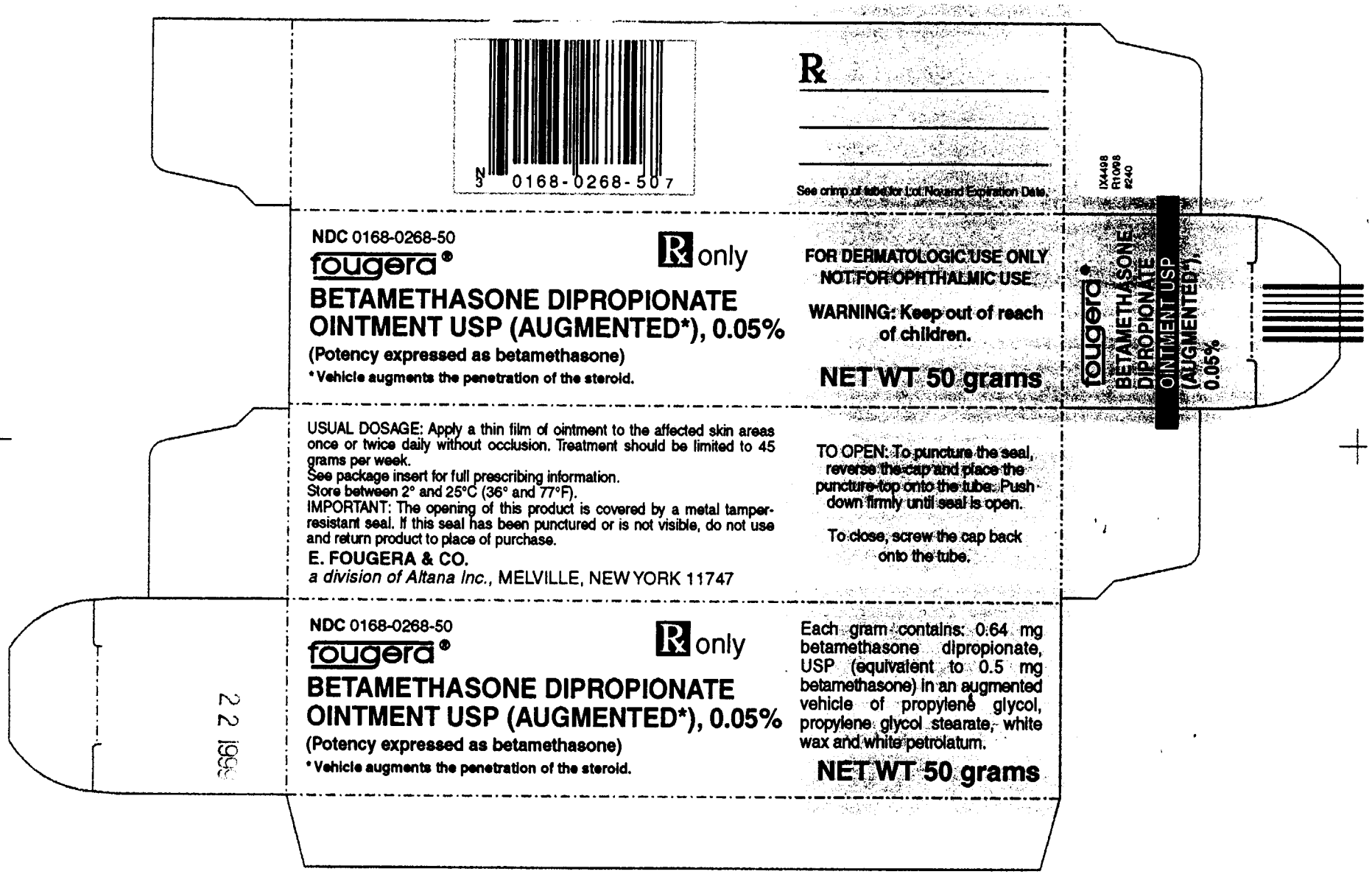
Betamethasone dipropionate ointment (augmented) is not to be used with occlusive dressings.

HOW SUPPLIED: Betamethasone Dipropionate Ointment USP (Augmented*), 0.05%, is supplied as follows:
NDC 0168-0268-15 15 gram tube NDC 0168-0268-50 50 gram tube

Store between 2° and 25°C (36° and 77°F).

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

I268
#240
R10/98



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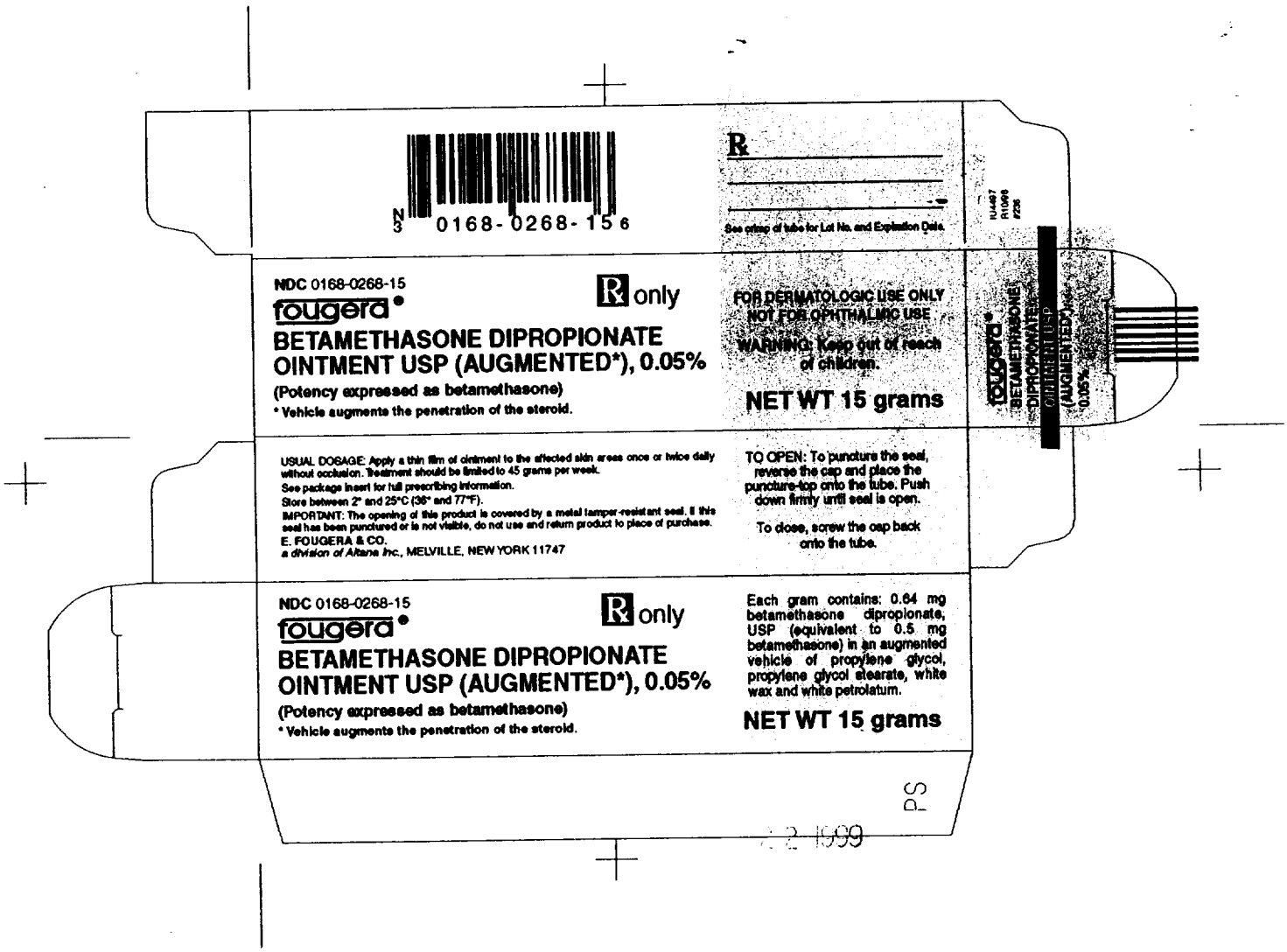

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Item #:IU4497	Colors: Yellow, Black
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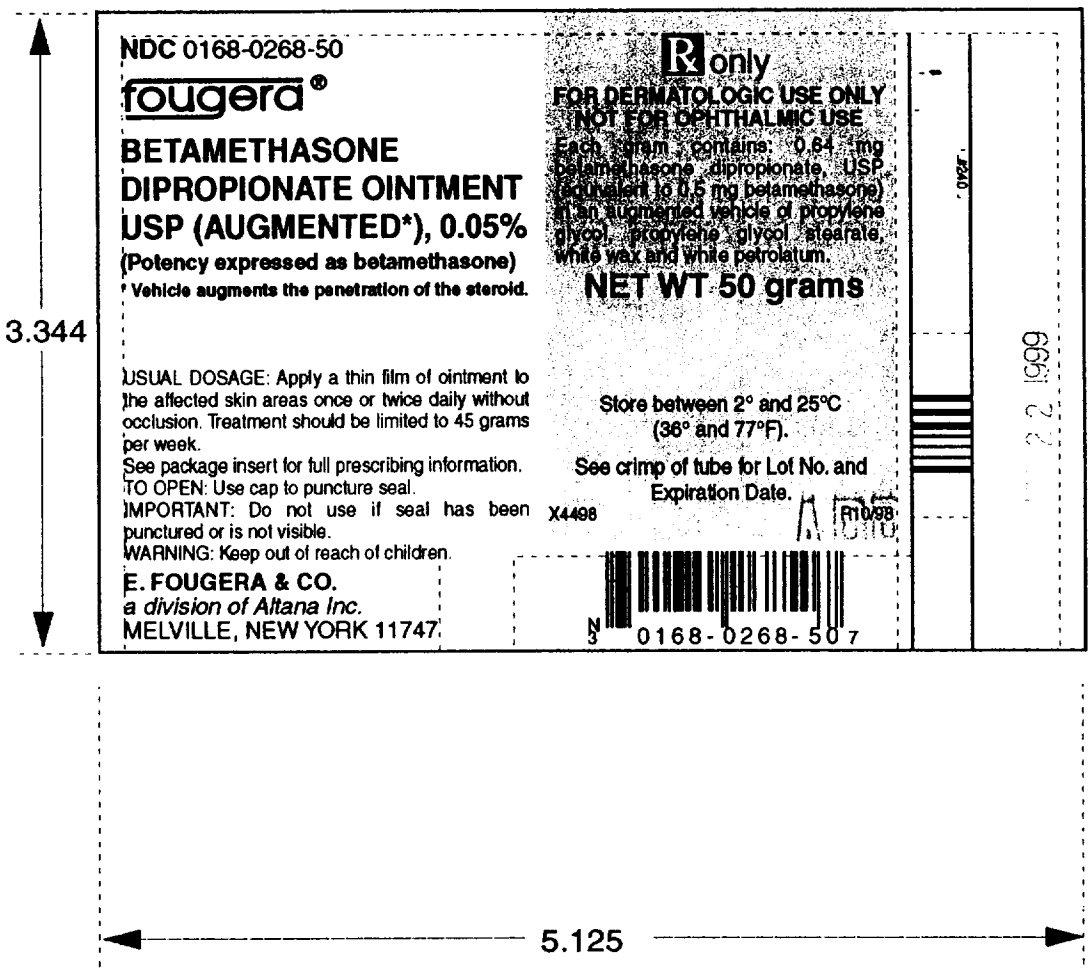
mango

Waiting for conformation on die placements



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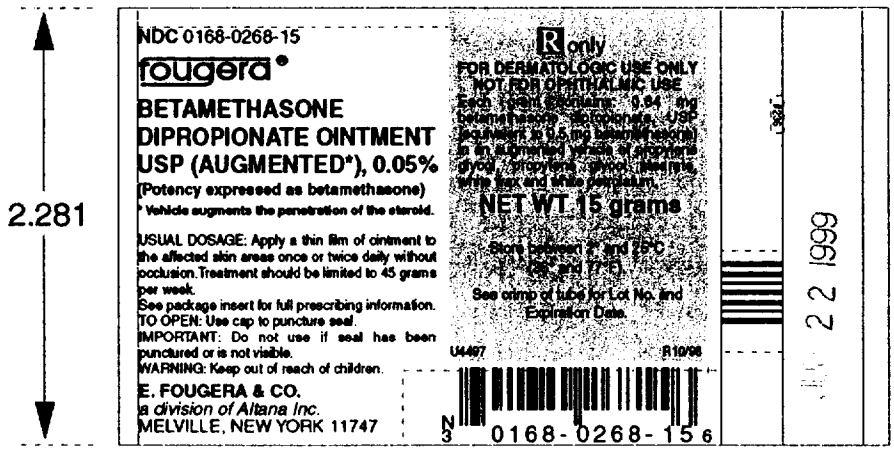


15 grams Tube Temp.

Drawing LB-518

Item: Betamethasone Dipropionate OINT 0.05% Augmented	
Item #:U4497	Colors: Yellow, Black
Die Size: 4 x circ 2.281	Pharma# 236

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-373

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-373

3. NAME AND ADDRESS OF APPLICANT

Altana Inc.
60 Baylis Road
Melville, NY 11747

4. LEGAL BASIS FOR SUBMISSION

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

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Betamethasone Dipropionate

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

N/A

9. AMENDMENTS AND OTHER DATES:

Original 5/1/98
Amendment 11/5/98
Amendment 1/29/99 (Bio)
Amendment 3/31/99 5/26/99

10. PHARMACOLOGICAL CATEGORY

Anti inflammatory-steroid

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

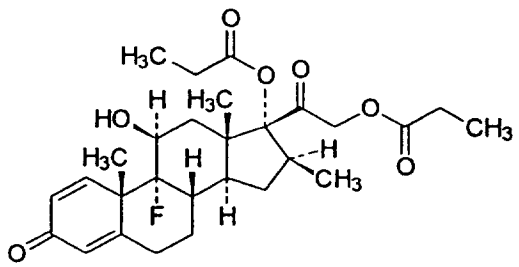
Ointment (Augmented)

14. POTENCY

0.05%

15. CHEMICAL NAME AND STRUCTURE

Betamethasone Dipropionate. Pregna-1,4-diene-3,20-dione, 9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, (11β,16β)-. $C_{28}H_{37}FO_7$. M.Wt. 504.6. 5593-20-4. Glucocortic. USP 23, page 190.



16. RECORDS AND REPORTS

17. COMMENTS

The firm has withdrawn the drug substance manufacturer Roussel UCLAF DMF 7389.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 5/27/99

Supervisor: Paul Schwartz, Ph.D. 6/8/99

cc:

Endorsements:

Page(s) 10

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

clem Rev 3
5/27/99

MAR 23 1999

38. Chemistry Comments to be provided to the Applicant.

ANDA: 75-373 APPLICANT: ALTANA Inc.

DRUG PRODUCT: Betamethasone Dipropionate Ointment, USP (Augmented), 0.05%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please revise your in-process controls specification to include RSD limits for the blend uniformity assay test.

2. Based on your data, please revise your stability acceptance limits for degradation products.

3. Please provide a specification for the mean of the homogeneity test.

4. The DMF is deficient. The DMF holder has been notified.

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

Your bioequivalency amendment of January 29, 1999 is under review. Review comments will be provided at a later date.

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:

75-373

Bioequivalence Review(s)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-373 APPLICANT: Altana

DRUG PRODUCT: Augmented betamethasone dipropionate 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,

Dale P. Conner

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-373 APPLICANT: Altana

DRUG PRODUCT: Augmented betamethasone dipropionate 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,

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

Aug. Betamethasone Diprop. Oint., 0.05%
ANDA # 75-373
Reviewer: Nhan L. Tran
WP # 75373A.199

Altana Inc.
Melville, NY
Submission Date:
January 29, 1999

REVIEW OF AN AMENDMENT

The original submission was dated May 1, 1998. The Division of Bioequivalence has reviewed it on December 18, 1998, and found it incomplete. The firm is responding to the deficiencies in this amendment.

REVIEW OF THE RESPONSES

Deficiency 1: According to the Guidance for Dermatologic Corticosteroids, the use of ED50 from ChromaMeter measurement is recommended over the ED50 derived from the visual measurement. The Guidance also indicates that ED50 derived from visual assessment can be used if a correlation between ChromaMeter and visual measurement can be established. Such a correlation has not been established when the firm elects ED50 derived from visual assessments for use in the pivotal study.
Firm's Response: The firm stated that a combination of both visual and ChromaMeter data was used to determine the appropriateness of ED50 for the pivotal study. The Guidance specifically states that the ED50 may be rounded by up to 15 minutes to obtain a ED50 value for the pivotal study. Hence, if a ED50 calculated by the ChromaMeter was 27 minutes, it can be rounded to 42 minutes. This value is comparable to the ED50 estimated by visual assessment.
FDA's Comment: The response is acceptable.

Deficiency 2: Please indicate which method (naive pooled or population) was used in fitting SASMIXLIN.
Firm's Response: Population model was used in SASMIXLIN to estimate the Emax and ED50.
FDA's Comment: Acceptable.

Deficiency 3: The firm is requested to provide ED50 and Emax for visual and ChromaMeter assessments using programs other than SASMIXLIN, such as P-Pharm or NONMEM, with naive pooling and population methods.
Firm's Response: Additional analyses were performed as requested. Results indicated that there is no significant difference in the estimation of ED50 regardless of softwares or methods used.
FDA's Comment: The reviewer has reviewed the information submitted and found the response acceptable.

Deficiency 4: Mean plots (observed and predicted) along with individual plots for all subjects in the study should be provided.
Firm's Response: Data was provided as requested.
FDA's Comment: Mean plots as well as individual plots for all subjects were submitted in this amendment. Information was reviewed and found acceptable.

Deficiency 5: What are the units of the visual and ChromaMeter areas?
Firm's Response: There is no unit for either visual or ChromaMeter assessment. One scale is a finite subjective scale, the other is a infinite objective scale for which no units are available. In addition, the Guidance also does not provide any units for those assessments.
FDA's Comment: The response is acceptable.

Deficiency 6. Pivotal Study: The firm should explain in detail how data from the pivotal study is statistically analyzed.
Firm's Response: Locke's method was used for the calculation of confidence intervals of visual scoring and ChromaMeter assessment, as suggested in the Guidance.
FDA's Comment: Acceptable.

Summary and Conclusion : The firm has responded adequately to the FDA deficiencies. Mean results for visual and ChromaMeter evaluation of Altana's product(Test) and Diprolene Ointment (Reference) using Locke's Method for calculating confidence intervals are shown in the table below.

Mean Results for Visual and ChromaMeter Evaluation of Altana's Product(Test) and Diprolene Ointment (Reference).

	N	Means		Ratio	90% C.I.
		Test	Ref.	(%)	
Visual	51	26.79	28.28	94.7	90.8% - 98.8%
Chroma.	42	27.50	28.23	97.4	91% - 104.4%

Based on the data submitted, the reviewer has verified the results and concluded that the firm's calculation and the reviewer' s results are in good agreement.

Recommendation

The ***in-vivo*** bioequivalence study using pharmacodynamic end points conducted by Altana Inc., comparing its augmented betamethasone dipropionate ointment, 0.05%, Lot #A007, to Diprolene^R augmented ointment 0.05% manufactured by Schering Corporation, Lot # 6HYA503, has been found acceptable. The results of the vasoconstrictor study demonstrate that Altana's augmented betamethasone dipropionate ointment, 0.05%, is bioequivalent to Diprolene^R augmented ointment 0.05% manufactured by Schering Corporation.

Nhan L. Tran, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED SNerurkar
FT INITIALED SNerurkar 4/22/1999

Concur: Date: 4/27/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Aug. Betamethasone Diprop. Oint., 0.05%
ANDA # 75-373
Reviewer: Nhan L. Tran
WP # 75373S.598

Altana Inc.
Melville, NY
Submission Date:
May 1, 1998
August 19, 1998
August 25, 1998

REVIEW OF TWO TOPICAL CORTICOSTEROID BIOEQUIVALENCE STUDIES

Indication: Topical Corticosteroid
Submission: Not A First Generic
Content of Submission: A Pilot study and A Pivotal Study
ANDA Status: Original

Brief Background Information: Betamethasone dipropionate is a synthetic adrenocorticosteroid for dermatologic use. It is effective in the treatment of corticosteroid-responsive dermatoses primarily because of its anti-inflammatory, anti-pruritic, and vasoconstrictive actions. According to the FDA Guidance for Topical Corticosteroid Drug Products, to demonstrate the bioequivalence of the test and the reference listed product [Diprolene^R augmented ointment 0.05% manufactured by Schering Corporation], the firm is required to conduct a pilot dose duration-response study on the REFERENCE product, and a comparative, randomized, pivotal bioequivalence vasoconstrictive study on the test and reference drug products.

PILOT DOSE DURATION-RESPONSE STUDY REFERENCE PRODUCT ONLY

A. Study Information:

Protocol #:	
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	Novum Pharmaceutical Research Services
Principal Investigator:	A. Miro, M.D.
Assessments:	**ChromaMeter and Visual**
Statistics:	Novum Pharmaceutical Research Services
Study Dates:	January 10 - 11, 1998
Study Design:	One period dose response-duration study.
Treatments:	
Reference product:	Diprolene^R augmented ointment 0.05% manufactured by Schering Corporation, Lot # 6HYA503, expiration date: 6/98.
Test Product:	**Not required.**

Subjects: Fifteen subjects who were chosen for participation in this study were healthy, asymptomatic, non-tobacco-users (for 30 days prior to dosing), fair-skinned women in the age range of 18 to 47 years. They were within 15 % of their ideal weight as specified in the protocol. They were enrolled according to the inclusion/exclusion criteria as specified in the protocol.

Housing: From -12 hours to 24 hours post-dose

Dosing Procedures: 10 microliter (μl) of Diprolene^R ointment was applied to the 7 assigned sites on each arm at 5, 10, 15, 30 minutes, and 1, 2, 3 hours prior to removal. All applications were removed at the same time point with the shortest duration removed first. The residue was removed by wiping with a cotton ball, and the untreated site (control) on each arm was wiped in the same way with a clean cotton ball.

Assessments: Chromameter assessment always precedes visual assessment. Chromameter operators and visual evaluators assessed the degree of blanching response at each site prior to treatment application and at 0, 2, 4, 6, 8, 10, 12, 20, and 24 hours after removal.
ChromaMeter. The **ChromaMeter** was used in this study to measure the reflective colors from the skin surface. Chromameter assessments were based on the a-scale response.
Visual: Visual scoring used the following rating scale: 0=no change from surrounding area, 1=slight outline of application site, 2=discernible, and 3=distinct outline of application site.

B. Study Results:

1. Clinical:

Drop-outs: None reported.

Adverse Events: None reported.

Protocol Deviations: None reported.

2. Validation

Validation: ChromaMeter: Prior to the study, precision of the chromameter operator was evaluated from replicate evaluations. **SAS Proc Varcomp** was used to determine between site and within site %CV for different operators as follows:

Date	Evaluator	%CV within site	%CV between site
10-17-96	**LMM**	**7.5%**	**5.6%**
	MEB	6.5%	6.2%
09-19-96	**LMM**	**5.4%**	**8.3%**
	RP	6.3%	8.3%
09-07-95	**LMM**	**5.4%**	**12.1%**
	RWM	6.2%	12.9%

RWM was selected as chromameter evaluator.

%CV between and within sites were not reported for visual assessment.

3. Data Evaluation: Data for chromameter and visual assessments are given in the Appendix. Mean results and Emax model parameter estimates for visual and chromameter areas (N=15) as **reported by the firm** as follows:

Duration (min.)	Visual	Chromameter
5	11.5	10.2
10	10.1	17.0
15	15.1	16.6
30	20.1	22.1
60	29.1	36.
120	44.2	44.5
180	44.9	44.0
Emax	55.1	51.6
%CV	10.6	11.7
ED50	40.2	27.0
%CV	21	21

According to the firm, the ED50 and Emax parameters were estimated using a population fitting technique. The data was fit to the simple Emax model: E=[(Emax*D)/(ED50+D)] using SAS macro MIXLIN, where E is the response (area) at D, the duration of application, and ED50 is the duration at which half-maximal response occurs. The firm indicated that, in the pivotal study, the ED50 from **visual assessment** was used, while the Guidance for Dermatologic Corticosteroids (page 6), on the other hand, recommends ED50 from chromameter measurement be used. The Guidance also indicates that if ED50 derived from visual measurement is used in the **pivotal** study, a correlation between chromameter and visual measurements should be established first. Hence, per Guidance for Dermatologic Corticosteroids, establishment of a correlation (if any) between visual and chromameter assessments is necessary, if ED50 derived from visual assessment is going to be used in the pivotal study.

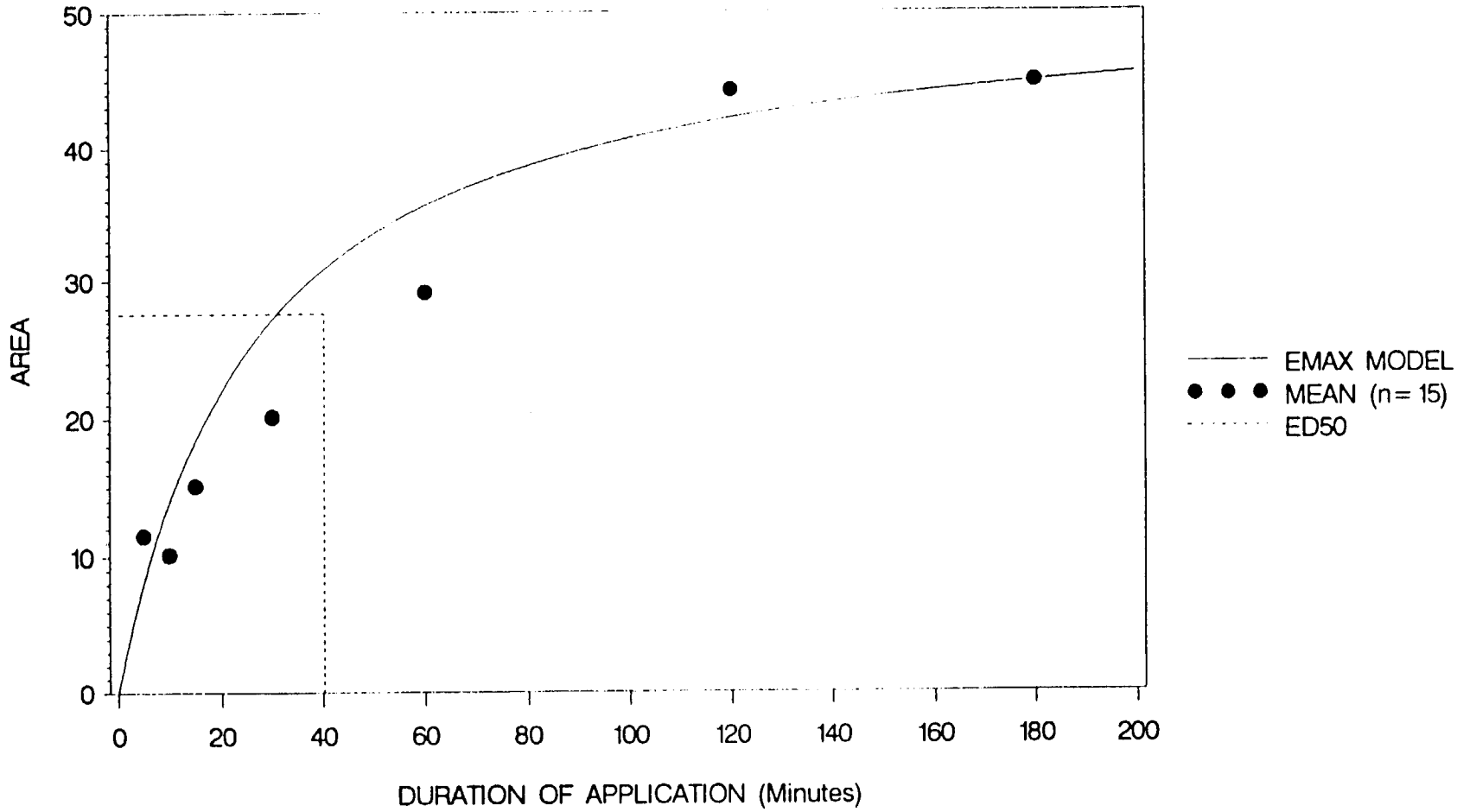
Deficiencies--Pilot Study: (see under Deficiencies)

PIVOTAL IN-VIVO BIOEQUIVALENCE STUDY

A. Study Information:

Protocol #:	
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	Novum Pharmaceutical Research Services
Principal Investigator:	A. Miro, M.D.
Assessments:	**ChromaMeter and Visual**
Statistics:	Novum Pharmaceutical Research Services
Study Dates:	Subj 1-22: January 17, 1998. Subj 23-44: January 24, 1998. Subj 45-60: January 31, 1998.
Study Design:	One period, randomized, vasoconstrictor.

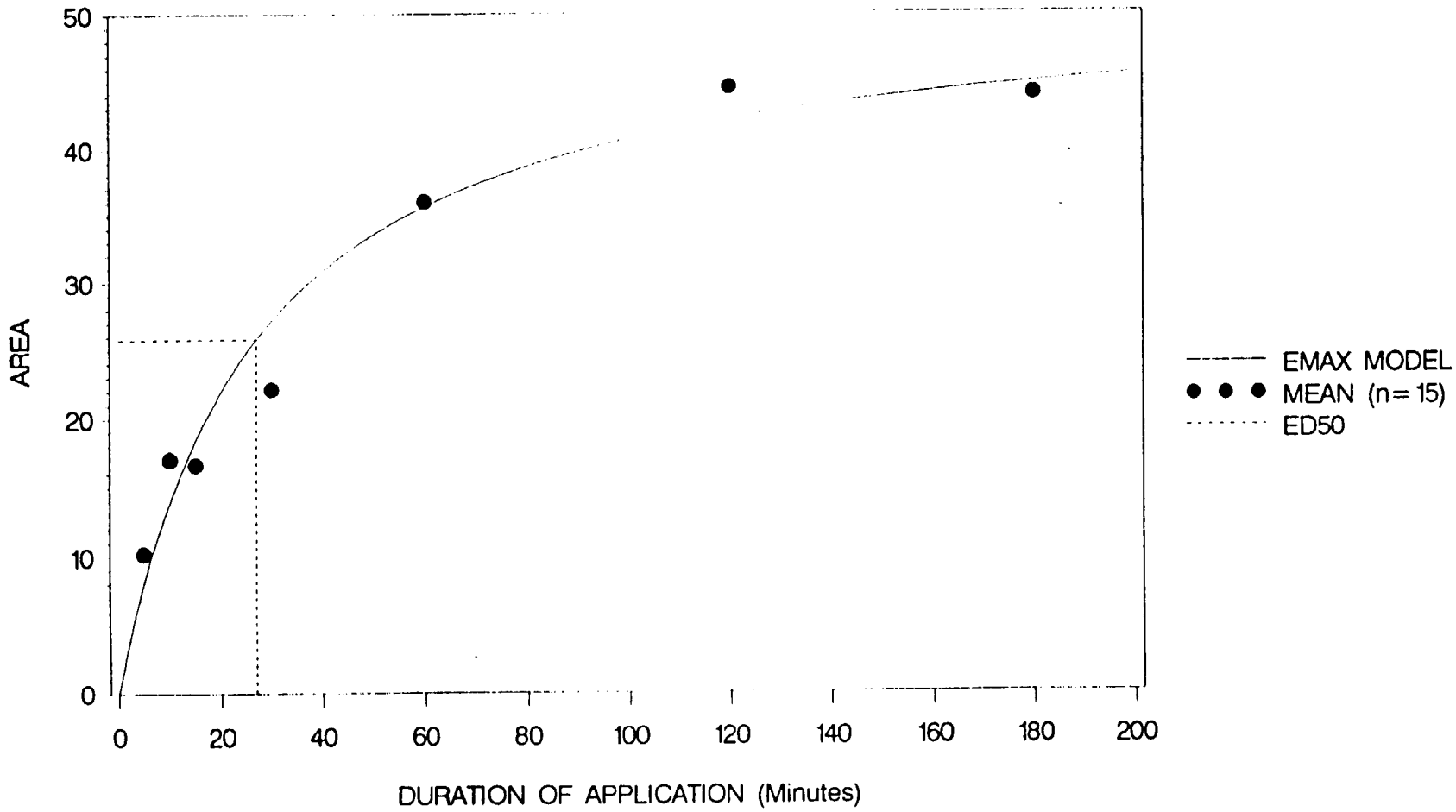
AUGMENTED BETAMETHASONE DIPROPIONATE STUDY NO. 9728211
VISUAL AREA UNDER THE RESPONSE CURVE vs DURATION OF APPLICATION
(EMAX = 55.14 ED50 = 40.17)



AUGMENTED BETAMETHASONE DIPROPIONATE STUDY NO. 9728211

CHROMAMETER –AREA UNDER THE RESPONSE CURVE vs DURATION OF APPLICATION

(EMAX = 51.61 ED50 = 26.93)



Treatment:
Reference product: Diprolene^{R} augmented ointment 0.05% manufactured by Schering Corporation, Lot # 6HYA503, expiration date: 6/98. Potency: 98.5%
Test Product: Augmented betamethasone dipropionate topical ointment 0.05%, manufactured by Altana, Inc., Lot # A007, manufacture date: 5/97. **Potency: 102%.**
Subjects: Sixty subjects who were chosen for participation in this study were healthy, asymptomatic, non-tobacco-users (for 30 days prior to dosing), fair-skinned women in the age range of 18 to 48 years. They were within 15 % of their ideal weight as specified in the protocol. They were enrolled according to inclusion /exclusion criteria as specified in the protocol.
Housing: From -12 hours to 24 hours post-dose
Dosing Procedures: 10 microliter (μl) of each test and reference formulations was applied to the assigned sites on each arm at 20, 40 or 80 minutes prior to removal. All applications were removed at the same time point with the shortest duration removed first. The residue was removed by wiping with a cotton ball, and the untreated site (control) on each arm was wiped in the same way with a clean cotton ball.
Assessments: Chromameter assessment always precedes visual assessment. Chromameter operators and visual evaluators assessed the degree of blanching response at each site prior to treatment application and at 0, 2, 4, 6, 8, 10, 12, 20, and 24 hours after removal.
ChromaMeter. The **ChromaMeter** was used in this study to measure the reflective colors from the skin surface. Chromameter assessments were based on the a-scale response.
Visual: Visual scoring used the following rating scale: 0=no change from surrounding area, 1=slight outline of application site, 2=discernible, and 3=distinct outline of application site.

B. Study Results:
1. Clinical:
Drop-outs: One (1) subject (#55) due to headache.
Adverse Events: 4 events reported in 3 subjects (#17, 48 and 55).
Protocol Deviations: None reported.
2. Data Evaluation: The post dose **VISUAL** readings at each site were adjusted by subtracting the untreated site readings from the treated sites for each arm. The post dose **CHROMAMETER** readings at each site (corrected baseline-adjusted value) were adjusted by subtracting the mean baseline-adjusted value for the untreated sites on each arm from the baseline-adjusted chromameter value for each site on the same arm at each assessment time. The areas under the response curves for the visual assessments were determined directly from the raw blanching scores of the evaluator. Chromameter areas under the response curve from 0-24 hours were calculated from the corrected baseline-adjusted reading by linear trapezoidal method. Only subjects whose D2/D1 was at least 1.25 were considered qualified for inclusion in the statistical analyses. A subject whose mean D1 value indicated non-blanching but whose D2 showed blanching could also qualify for inclusion if the ratio of the subjects D2 to ED50 response for the reference was at least 1.25.
Statistical Analyses: Lockes method for calculating confidence intervals was applied to the visual scoring and chromameter results of the qualifying detectors.

Results: 51 subjects qualified for inclusion in the visual analyses by the D2/D1 criteria; and in the analyses of the chromameter data, 42 subjects qualified for inclusion by the D2/D1 criteria. The results of from the analyses of both data are summarized below.

Mean Results for Visual and Chromameter Evaluation of Altana's Product(Test) and Diprolene ointment (Reference).

	N	Means		Ratio	90% C.I.
		Test	Ref.	(%)	
Visual	51	26.79	28.28	94.7	[0.91;0.99]
Chroma.	42	27.50	28.23	97.4	[0.91;1.04]

III. In Vitro Testing: Not required.
IV. Formulation Comparison

DO NOT RELEASE THE FOLLOWING INFORMATION UNDER FOI.

The comparative formulation of the test and the reference products are presented below:

Ingredients	Test Product	Ref. Product
Betamethasone Dipropionate		e
Propylene Glycol		
Propylene Glycol Stearate		

;

V. Deficiencies

Pilot Study

1. According to the Guidance for Dermatologic Corticosteroids, the use of ED50 from chromameter measurement is recommended over the ED50 derived from the visual measurement. The Guidance also indicates that ED50 derived from visual assessment can be used if a correlation between chromameter and visual measurement can be established. Such a correlation has not been established when the firm selects ED50 derived from visual assessments in the pivotal study.
2. Please indicate which method (naive pooled or population) was used in fitting SASMIXLIN.
3. The firm is requested to provide ED50 and Emax for visual and chromameter assessments using programs other than SASMIXLIN (a SAS macro), such as P-Pharm or NONMEM, with naive pooling and population methods.
4. Mean plots (observed and predicted) along with individual plots for all subjects in the study should be provided.

5. What are the units of the visual and chromameter areas?

Pivotal Study

The firm should explain in detail how data from the pivotal study is statistically analyzed.

V. Recommendation

The in-vivo pharmacodynamic study conducted by Altana comparing the test product, Altana's Augmented Betamethasone Dipropionate Topical ointment, 0.05%, to the RLD product, Diprolene Topical Ointment, 0.05%, manufactured by Schering has been found to be incomplete to the Division of Bioequivalence due to Deficiencies above.

Nhan L. Tran
Division of Bioequivalence
Review Branch II

for 12/17

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

Concur: _____ Date: 12/18/98

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

c
File, Division File

Page(s) 5

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

5/1/95

Raw Data

BIOEQUIVALENCY COMMENTS

ANDA: 75-3763 APPLICANT: Altana Inc.

DRUG PRODUCT: Augmented Betamethasone Dipropionate 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. According to the Guidance for Dermatologic Corticosteroids, the use of ED50 from chromameter measurement is recommended over the ED50 derived from the visual measurement. The Guidance also indicates that ED50 derived from visual assessment can be used if a correlation between chromameter and visual measurement can be established. Such a correlation has not been established when ED50 derived from visual assessments was selected for use in the pivotal study.
2. Please indicate which method (naive pooled or population) was used in fitting SASMIXLIN.
3. Using naive pooled and population methods, please provide ED50 and Emax for visual and chromameter assessments using programs other than SASMIXLIN, such as P-Pharm or NONMEM.
4. Mean plots (observed and predicted) along with individual plots for all subjects in the study should be provided.
5. Please indicate the units of the visual and chromameter areas.

Pivotal Study

Please explain in detail how data from the pivotal study is statistically analyzed.

Sincerely yours,

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

DEC 30 1998

BIOEQUIVALENCY COMMENTS

ANDA: 75-373 APPLICANT: Altana Inc.

DRUG PRODUCT: Augmented Betamethasone Dipropionate 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. According to the Guidance for Dermatologic Corticosteroids, the use of ED50 from chromameter measurement is recommended over the ED50 derived from the visual measurement. The Guidance also indicates that ED50 derived from visual assessment can be used if a correlation between chromameter and visual measurement can be established. Such a correlation has not been established when ED50 derived from visual assessments was selected for use in the pivotal study.
2. Please indicate which method (naive pooled or population) was used in fitting SASMIXLIN.
3. Using naive pooled and population methods, please provide ED50 and Emax for visual and chromameter assessments using programs other than SASMIXLIN, such as P-Pharm or NONMEM.
4. Mean plots (observed and predicted) along with individual plots for all subjects in the study should be provided.
5. Please indicate the units of the visual and chromameter areas.

Pivotal Study

Please explain in detail how data from the pivotal study is statistically analyzed.

Sincerely yours,

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:

75-373

CORRESPONDENCE

ALTANA

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

March 31, 1999

VIA FEDERAL EXPRESS

ORIG AMENDMENT
N/AM
4/6/99
AM mailed
To Chemistry reviewer
for review.

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, MD 20855-2773

Re: ANDA 75-373 **MINOR AMENDMENT**
Betamethasone Dipropionate Ointment USP, (Augmented) 0.05%

Dear Dr. Patel:

Reference is made to our original Abbreviated New Drug Application submitted May 1, 1998, our amendment of November 5, 1998, as well as the Agency's chemistry and labeling communications of October 21, 1998 and March 23, 1999.

We wish to respond to each comment of the March correspondence as follows:

A. Deficiencies

1.

2.

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4-5-99

3.

4.

Response

B. We also acknowledge that our bioequivalency amendment of January 29, 2999 is under review, and any review comments will be provided at a later date.

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

Sincerely,
Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

VC/isf

VC:Rashmikant Patel ANDA 75-373

ALTANA

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

FEDERAL EXPRESS

January 29, 1999

NDA ORIG AMENDMENT

AB

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

RE: ANDA 75-373 BIOEQUIVALENCY AMENDMENT
Augmented Betamethasone Dipropionate Ointment, 0.05%

Dear Dr. Connor:

Reference is made to your communication of December 30, 1998 (copy attached) requesting additional information on our bioequivalency study.

This study was performed for us by Novum Inc. Pittsburgh, PA. They have performed several similar studies for us, one of which has been approved, and we have a letter of acceptance from the Division for two pending applications.

Novum has indicated that using the exact same methodology they have had several approvals in 1998 for other clients besides Altana.

The letter has been responded to by Novum, as the CRO. Therefore in the responses where the word "we" appears, it refers to Novum Inc.

Pilot Study

1. Comment

According to the Guidance for Dermatologic Corticosteroids, the use of ED50 from chromameter measurement is recommended over the ED50 derived from the visual measurement. The Guidance also indicates that ED50 derived from visual assessment can be used if a correlation between chromameter and visual measurement can be established. Such a correlation has not been established when ED50 derived from visual assessments was selected for use in the pivotal study.

RECEIVED

FEB 1 1 1999

GENERIC DRUGS

Response

As both variables are used in the bioequivalency study, we use a combination of both visual and ChromaMeter data to determine an appropriate ED50 for the full study. The most important aspect of choosing an ED50 is that it be appropriate to differentiate "responders" in the bioequivalence study and also be the practical from an operational perspective. The ED50 calculated by the ChromaMeter was 27 minutes and by visual 40 minutes. Based on all the information available, an ED50 of 40 minutes was considered the most suitable for this bioequivalence study. In addition, the Guidance specifically states that the "ED50 may be rounded by up to 15 minutes to obtain the ED50 value used in the pivotal study". Therefore, if only the ChromaMeter data were used, according to the Guidance even an ED50 of up to 42 minutes would be acceptable.

The correctness of this value can be confirmed in that in the bioequivalence study 72% of the subjects in the ChromaMeter data set and 84% of the subjects in the visual data set met the "responder" criteria. If the ED50 is incorrectly calculated the responder rates become very low and the full bioequivalence study impossible to conduct.

2. **Comment**

Please indicate which method (naïve pooled or population) was used in fitting SASMIXLIN.

Response

A population model was used to estimate the Emax and ED50 parameters and this is clearly stated on "Page 5 Section VI Date Evaluation and Results" of the Final Report (copy included at Attachment A).

3. **Comment**

Using naïve pooled and population methods, please provide ED50 and Emax for visual and chromameter assessments using programs other than SASMIXLIN, such as P-Pharm or NONMEM.

Response

The Guidance specifically states that either a population model or a naïve pooling data method are suitable. We have had previous discussions with FDA on which they prefer and understand that the population model is currently preferable. Since the middle of 1997 we have been using this model on which to base the ED50, although the naïve pooling data was included in the report

(copies of relevant pages attached, Attachment B) we saw no need to refer to it in the text. As you will note, the values are almost identical to those calculated using the population model.

For your information, when the ED50 is very short i.e. with the higher potency products, then using the population model will tend to slightly lengthen the ED50 compared to the naïve pooling method.

We have always used the SAS macro MIXNLIN in previous studies, and this has never been questioned by OGD. If the Agency is now insisting that specific trade software be used for the analysis, I think that this should be made through a public statement, as this then becomes a specific product endorsement.

However, as requested we have re-run the dose-response data both on NONMEM (Attachment C) and on P-Pharm (Attachment D). The calculated ED50s are 45 and 44 minutes for the visual and 26 and 20 minutes for the ChromaMeter when calculated using NONMEM and P-Pharm respectively. As is clearly apparent, the different algorithms lead to only minimal different estimates of ED50, which are obviously not significant in the estimation of the ED50 for the pivotal study. As we have now had to calculate eight different ED50s for this study, I have provided a summary table (Attachment E).

As this exercise clearly demonstrates, and about which I know the FDA is already aware, the ED50, however calculated, is only an estimate for identifying the duration's of application for the full study. As already stated in my reply to Item 1, an incorrectly calculated ED50 would lead to an unworkable bioequivalency study. Somewhere between 30 to 45 minutes is without any doubt the correct ED50 for this product, and is also consistent with the potency classification for this product.

4. Comment

Mean plots (observed and predicated) along with individual plots for all subjects in the study should be provided.

Response

Again I am assuming this is a new request from the FDA as we have never been asked for this before, nor is it requested in the Guidance. Full data listings are provided in the report. But I have provided the plots as requested (Attachment F).

5. Comment

Please indicate the units of the visual and chromameter areas.

Response

There are no units for either variable. One scale is a finite subjective scale (visual), the other a potentially infinite objective scale for which no units are available (ChromaMeter). You will note no units are provided in the Guidance for this very reason.

Pivotal Study

Comment

Please explain in detail how data from the pivotal study is statistically analyzed.

Response

The Pivotal Study report contains a full page "Page 6, Section VI. Data Evaluations and Results" detailing all aspects of the data analysis. I have attached a copy of the relevant page and the reference cited within (Attachment G).

Additionally, please find included with this information a diskette containing the reanalysis of the dose response study using P-Pharm.

We trust that this additional information will allow the Division to complete its review of our bioequivalence study and come to a favorable decision concerning our drug product.

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

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

Enclosure

VC:pj

ALTANA

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

Federal Express

FPL

ENT

November 5, 1998

N/AC

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
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, MD 20855-2773

Re: ANDA 75-373 **MAJOR AMENDMENT**
Betamethasone Dipropionate Ointment USP Augmented, 0.05%

Dear Dr. Patel:

Reference is made to our original Abbreviated New Drug Application submitted May 1, 1998; pursuant to Section 505(j) of the Act.

Reference is also made to the Agency's telefax of October 21, 1998, in which several deficiencies were noted in our application.

We wish to respond to the Agency's concerns as follows:

A. Deficiencies

Comment

1. Please provide test, procedure and acceptance limits for residual solvents and individual impurities in the drug substance.

Response

Revised specifications containing acceptance limits for residual solvents and individual impurities in the drug substance may be found in Attachment 1. Analytical Procedures can be found in Attachment 2. Test results for the active

drug substances (lots 9610000133, 9612000053) used to support this application are found in Attachment 3.

At this time we wish to add an additional analytical laboratory to perform residual solvents and impurity testing:

A GMP compliance statement for is included in Attachment 4.

Comment

Comment

3.

Page(s) _____

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

11/5/98

Response

B. In addition to the responses to the noted deficiencies we also acknowledge:

Comment

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

2. Our bioequivalence study is under review and further comments may result.

3. Our analytical methods will be submitted for validation at an FDA District Laboratory. We will submit samples promptly when requested.

Labeling Deficiencies:

1. General Comment

   a. The established name of this product is Betamethasone Dipropionate Ointment. Throughout your labeling, please refer to your drug product as betamethasone dipropionate ointment (augmented).

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

2. Container (15 g and 50 g)

   This product is the subject of a USP monograph. The established name should be represented as follows: Betamethasone Dipropionate Ointment USP (Augmented)

Response

Revised container labeling which incorporates the USP established name is included in Attachment 13.

Comment

3. Carton (15 g and 50 g)

   a. See General Comment (a).

b. See Container Comment.

Response

Revised carton labeling which incorporates the USP established name is included in Attachment 14.

Comment

4. Insert

a. General Comment

Revise to delete the strength, "0.05%", appearing with the established name of your product throughout the text except the product title and HOW SUPPLIED section.

b. Description

Revise the first sentence of the second paragraph to read, ...molecular formula...rather than....empirical formula....

c. Clinical Pharmacology (Pharmacokinetics)

Revise the second sentence of the first paragraph to read, ...disease processes....

d. Precautions

i. Pregnancy

Revise the penultimate sentence to read, ...risk to the fetus

ii. Nursing Mothers

Revise the penultimate sentence to read, ...breast milk in...

iii. Pediatric Use

Revise the first paragraph to read, ...in pediatric patients under....

e. Adverse Reactions

i. Revise to delete the first paragraph.

ii. Revise the make the following the second paragraph:

The following adverse reactions have also been reported with betamethasone dipropionate ointment (augmented): erythema and vesiculation.

Response

Revised insert labeling which incorporates all of the FDA's requests is included in Attachment 15.

A side-by-side comparison of our proposed labeling and our originally submitted labeling is included as follows:

Container	Attachment 16
Carton	Attachment 17
Insert	Attachment 18

We acknowledge that the Agency reserve the right to request further changes in our labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

We trust that with this additional information the Agency will deem our application approvable.

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

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

VC:pj
Encl.

ALTANA

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

FEDERAL EXPRESS

ANDA AMENDMENT

BIOEQUIVALENCE DISKETTE

August 18, 1998

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

RE: ANDA 75-373 Telephone Amendment
Augmented Betamethasone Dipropionate Ointment, 0.05%

Dear Mr. Sporn:

As per a request from the Division of Bioequivalence please find enclosed a diskette which includes the data from the bioequivalency study comparing our product to Diprolene (betamethasone dipropionate augmented) Ointment (Schering).

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

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

Enclosure

VC:pj

ALTANA

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

May 15, 1998

Ms. Denise Huie
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

VIA TELEFAX (301) 594-1174
AND FEDERAL EXPRESS

NEW CORRESP
NC

Augmented Betamethasone Dipropionate Ointment, 0.05%
ANDA 75-373
Facsimile Amendment

Dear Ms. Huie:

Reference is made to the abbreviated new drug application for Augmented Betamethasone Dipropionate Ointment, 0.05%, ANDA 75-373 submitted on May 1, 1998 pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Altana Inc. is submitting this Amendment in response to the FDA telephone request on May 14, 1998. The information is presented in **comment**/response format.

Reconciliation for the Executed Batch Records: How much bulk product was manufactured and how was it distributed between the 15 and 50 gram tubes?

The reconciliation for the Augmented Betamethasone Dipropionate Ointment, 0.05% exhibit batches Lot Nos. A007 and A008 can be found on pages 1651 and 1740, respectively, in the original ANDA submission. For ease of review copies of these pages and a summary of the reconciliations have been included in this amendment.

If you require any additional information please contact me at (516) 454-7677 extension 2092.

Sincerely,

Altana Inc.

Cynthia I. Renger

Cynthia I. Renger
Associate Director, Regulatory Affairs

CIR/ab

A:\ANDA75-373amend.wpd

RECEIVED
MAY 19 1998
GENERIC DRUGS

ALTANA

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

Federal Express

May 1, 1998

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
Augmented Betamethasone Dipropionate 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, Augmented Betamethasone Dipropionate Ointment, 0.05%.

The reference listed drug that is the basis for this submission is Diprolene ® (augmented betamethasone dipropionate ointment) 0.05% (NDA 18-741), manufactured by Schering Laboratories, Inc. The proposed drug, Augmented Betamethasone Dipropionate 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 batches (#A007, #A008) included in this application were fully packaged utilizing the 15 gram and 50 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 records.

Included in this six (6) volume submission, along with Form FDA 356h, is the required Patent Certification and Exclusivity statements, draft Labeling, Bioequivalence Study, 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:

Virginia Carman
Associate Director
Regulatory Affairs
Altana Inc.
60 Baylis Road
Melville, NY 11747
Tel. No. (516) 454-7677 Ext. 2091
Fax No. (516) 777-3916

A certified copy of this application (consisting of volumes 1.1, 1.5 and 1.6 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/ps

C:\Augmented Betamethasone Dipropionate Ointment 0.05%\COVER.LTR