CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER

CORRESPONDENCE

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, 1.4, 1.5 & 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/ab

C:\ANDAS\CLOBCRM.E\COVER.LTR

ALTANA

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

Federal Express

August 5, 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
Clobetasol Propionate Emollient Cream, 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, Clobetasol Propionate Emollient Cream, 0.05%.

The reference listed drug that is the basis for this submission is Temovate E™ (clobetasol propionate emollient cream) 0.05% (NDA 20-340), manufactured by Glaxo Wellcome. The proposed drug, Clobetasol Propionate Emollient Cream, 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 (#B156) included in this application was fully packaged utilizing the 15 gram, 30 gram, and 60 gram presentations for which approval is currently requested. The number of units filled of each package size and the disposition of any remaining bulk product are reconciled in the exhibit batch record.

Included in this 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,

ALTANA

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

Federal Express

August 5, 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
Clobetasol Propionate Emollient Cream, 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, Clobetasol Propionate Emollient Cream, 0.05%.

The reference listed drug that is the basis for this submission is Temovate E™ (clobetasol propionate emollient cream) 0.05% (NDA 20-340), manufactured by Glaxo Wellcome. The proposed drug, Clobetasol Propionate Emollient Cream, 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 (#B156) included in this application was fully packaged utilizing the 15 gram, 30 gram, and 60 gram presentations for which approval is currently requested. The number of units filled of each package size and the disposition of any remaining bulk product are reconciled in the exhibit batch record.

Included in this 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, 1.4, 1.5 & 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/ab

C:\ANDAS\CLOBCRM.E\COVER.LTR

ANDA 75-430

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

SEP 22 1998

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 September 9, 1998 and your correspondence dated September 11, 1998.

NAME OF DRUG: Clobetasol Propionate Cream USP, 0.05%

DATE OF APPLICATION: August 5, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 6, 1998

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:

Joe Buccine
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Jerry Phillips 7/22/98
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ALTANA

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

FEDERAL EXPRESS

September 11, 1998

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

NEW CORRESP
NC

RE: **ANDA 75-430 New Correspondence**
Clobetasol Propionate Emollient Cream, 0.05%

Dear Mr. Mahmud:

Reference is made to our telephone conversation of September 9, 1998 concerning the above noted application.

As per your request, please find enclosed, in duplicate, copies of Reference Listed Drug labeling for the 15 and 30 gram package sizes. These are in addition to the 60 gram labeling currently located in the application.

Also enclosed are revised Sections 3.1 (Patent Certification) 3.2 (Exclusivity Statement), and 10.2 (Function (of outside firms statement)).

We trust that with this additional information, the Office will find our application acceptable for filing.

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.

RECEIVED
SEP 15 1998
GENERIC DRUGS

ALTANA

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

Federal Express

March 19, 1999

NDA ORIG AMENDMENT
N/FA

Rashmikant 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, Maryland 20855-2773

RE: ANDA 75-430 TELEPHONE AMENDMENT
Clobetasol Propionate Cream, 0.05% (Emollient)

Dear Dr. Patel:

Reference is made to our amendment of March 17, 1999 and my telephone conversation with Dr. Paul Schwartz of the Division concerning the homogeneity specifications.

In our letter of March 17, 1999 we defined again the specification for homogeneity but did not address the limits to be set for the mean itself.

We have revised our specifications for both the finished product and stability samples. The mean itself must meet the assay specification of label value.

I apologize for this oversight.

Please find included with this cover letter copies of our two revised specifications.

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

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

VC:ab

Enclosures

C:\Virginia\ClobCrm. TelAmend. 3.19.99.wpd

RECEIVED
MAR 2 2 1999
GENERIC DRUGS

ALTANA

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

March 17, 1999

Rashmikant 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

NDA ORIG AMENDMENT
N/FA

Re: ANDA 75-430 TELEPHONE AMENDMENT
Clobetasol Propionate Cream, 0.05% (Emollient)

Dear Dr. Patel:

Reference is made to a telephone conference of March 17, 1999, between representatives of the Division and Altana in which specifications and stability data were discussed.

One of our specifications found in both the finished product and stability specifications is homogeneity. This specification is defined as "the clobetasol propionate assay values for the beginning, middle and end of the container are of the mean of the three values".

The homogeneity specification itself is based upon the requirements for homogeneity testing for Nitroglycerin Ointment USP as found in the USP (copy enclosed).

Additionally, we discussed an outlier found in the 3 month room temperature stability, and we were requested to explain the occurrence.

A summary of the laboratory's findings is included.

We trust that these additional explanations will allay any concerns regarding our product.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

Enc.

cc: Rashmikant Patel ANDA 75-430

RECEIVED
MAR 1 0 1999
GENERIC DRUGS

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

February 12, 1999

Rashmikant 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

NEW CORRESP
NC to
Fax

Re: ANDA 75-430 **FACSIMILE AMENDMENT**
Clobetasol Propionate Cream, 0.05% (Emollient)

Dear Dr. Patel:

Reference is made to our original Abbreviated New Drug Application dated August 5, 1998.

Reference is also made to the Agency's telefax of February 2, 1999 in which several deficiencies in our application were noted.

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

A. Deficiencies

1. Comment

Please revise the drug substance tests and specifications to include:

a. Residual solvent testing.

Response

Attachment 1 contains revised raw material specifications, which include residual solvent testing. Revised analytical procedures are included in Attachment 2. Results of residual solvent testing, performed on the lot of active drug substance used in the exhibit batch may be found in Attachment 3.

FEB 10 [illegible]

Please note: we will be using ories as an alternate contract testing laboratory for OVI and residual solvent testing. A copy of a letter indicating their adherence to CGMPs is included in Attachment 4.

2. Comment

Please revise the in-process tests and specifications:

a. Based upon the data submitted, tighten the viscosity specification.

b. Set the RSD limits for the clobetasol propionate assay.

c. Based upon the data submitted, reduce the specifications for individual and total degradants.

Response

The in-process specifications have been revised to tighten the viscosity specifications from cps to RSD limits for the clobetasol assay have been set at

The specifications for individual and total degradants have been reduced to each not more than and total to These correspond exactly to the USP specifications for clobetasol propionate drug substance. The revised specifications are included in Attachment 5.

3. Comment

Please revise the finished product tests and specifications:

a. Based upon the data submitted, tighten the viscosity specification.

b. Based upon the data submitted, reduce the specifications for individual and total degradants.

Response

The viscosity specification has been tighten from os to cps. The specifications for individual and total degradants have been reduced to each NM and total NMT As noted previously these conform to the USP specifications for the active drug substance. These specifications may be found in Attachment 6.

4. Comment

Please revise the stability specifications:

a. Based upon the data submitted, reduce the specifications for individual and total degradants.

b. Based upon the data submitted, tighten the viscosity specification.

c. Based upon the data submitted, reduce the weight loss specification.

Response

The specifications for the individual and total degradants have been revised to each NMF 1.0% and total NMT 2.5%.

The viscosity specification has been revised to ps. The weight loss specification has been reduced to Revised stability specifications may be found in Attachment 7.

Additionally, we have included updated room temperature stability data. Please see Attachment 8.

5. Comment

Please explain the finished product and stability homogeneity specification of "all assays fall within 90.0-110.0% of the mean".

Response

The specifications now read - the clobetasol propionate assay values for the beginning, middle and end of the container are 90.0% - 110.0% of the mean "of the three values". See Attachments 6 and 7.

6. Comment

Please describe the cycling conditions for the cycling stability study.

Response

Three cycles, each consisting of two days at 4°C followed by two days at 40°C were used. These conditions were recommended by Dr. Paul Schwartz of the OGD.

7. Comment

Please indicate the length of time the bulk product will be held before packaging.

Response

As per , bulk product will be held no longer than weeks before packaging.

Additionally, we wish to acknowledge the following:

1. The firms referenced in our application must be in compliance with CGMP at the time of approval.

2. Our bioequivalence study is under review, and that we will be notified of the findings under separate cover.

3. We have received the request for methods validation samples. These were submitted to the district laboratory February 2, 1999. A copy of our correspondence is included in Attachment 9.

4. The functions of each of the in-actives may be found in Attachment 10.

Labeling Deficiencies:

1. GENERAL COMMENTS

a. The established name of this drug product is "clobetasol propionate cream". The modifier "emollient" should appear separate from the established name.

b. Please note that your drug product is the subject of a USP monograph titled "Clobetasol Propionate Cream." We encourage you to include "USP" in conjunction with the established name on container labels, carton labeling, and the title of the package insert.

2. **CONTAINER (15g, 30g, 60g)**

Comments

a. See General Comments

b. Change the "Contains" statement to read, "Each gram contains: Clobetasol propionate 0.5 mg in..."

c. Include "Usual Dosage" before the "See package insert" statement (i.e., Usual Dosage: See package insert....).

d. Revise so that "See crimp for lot no. and... " uses a lower case "a".

Response

Revised container labeling which incorporates the Agency's comments is included in Attachment 11.

3. **CARTON (15g, 30g, 60g)**

Comment

a. See GENERAL comments.

b. See CONTAINER comments.

Response

Revised carton labeling may be found in Attachment 12.

4. **INSERT**

a. GENERAL COMMENTS

b. TITLE

Delete the asterisk and "*Potency expressed a clobetasol propionate".

c. DESCRIPTION

i. The molecular weight should read "466.98" to be in accord with USP 23.

ii. Revise the ultimate paragraph to read,

Each gram of clobetasol propionate cream (emollient) contains: clobetasol propionate 0.5 mg in an...

d. INDICATIONS AND USAGE

Add a space between "50" and "g" (i.e., 50 g) in the penultimate sentence.

e. PRECAUTIONS

i. General

A) Revise the ultimate sentence of the second paragraph to read, "...receiving super potent corticosteroids...".

B) Revise the penultimate sentence of the fourth paragraph to read, "...observing a failure...".

ii. Information for Patients

A) Revise the first sentence of the first paragraph to correct the spelling of "information".

B) Revise to add the following as instructions #6 and #7:

6. This medication should not be used on the face, underarms or groin areas.

7. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

iii. Pediatric Use

A) Revise the first sentence of the first paragraph to read, "have not been established and its use in pediatric patients under 12 years of age is not recommended."

B) Revise the penultimate sentence of the first paragraph to read, ...withdrawal of treatment. Adverse effects..."

C) Revise the ultimate sentence of the first paragraph to delete "(see PRECAUTIONS)".

f. ADVERSE REACTIONS

i. Revise the first sentence of the first paragraph to read, "In controlled trials with clobetasol propionate formulations..."

ii. Revise the ultimate sentence of the first paragraph to read:

The incidence of local adverse reactions reported in the trials with clobetasol propionate cream (emollient) was less than 2% of patients treated with the exception of burning/stinging which occurred in 5% of treated patients.

iii. Revise the first sentence of the second paragraph to read, "...of other topical clobetasol..."

g. DOSAGE AND ADMINISTRATION

i. Revise to add the following as the ultimate sentence of the second paragraph:

Use in children under 12 years of age is not recommended.

ii. Revise to delete the third paragraph of your submission.

Response

Revised insert labeling is included in Attachment 13.

As requested side-by-side comparisons of our proposed labeling with that previously submitted is included as follows:

Container	Attachment 14
Carton	Attachment 15
Insert	Attachment 16

We also note that the Agency reserves the right to request further changes in our labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

Please note we have a new facsimile number (516) 756-5114.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

VC/pj
Atts.