# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**75391**

## CORRESPONDENCE

ALTANA

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

January 20, 1999

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 2, Room 286
7500 Standish Place
Rockville, MD. 20855-2773

NDA ORIG AMENDMENT
N/FA

**RE: ANDA 75-391**
**Clobetasol Propionate Solution USP, 0.05%**

Dear Dr. Patel:

Reference is made to our original Abbreviated New Drug Application submitted May 27, 1998, as well as your facsimile amendment of December 9, 1998.

Reference is also made to a telephone conference between the OGD and Altana concerning our proposed stability specifications.

We were requested to revise the limits of the degradation products in our stability specifications. As per the Agency's request the individual degradation product specification was revised from NMT % to NMT % with the exception of the degradation product appearing at approximately this limit was set at NMT %. The limit for total degradation products was revised from NMT % to NMT %.

This information was also telefaxed to the office on this date.

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

Please note that our new telefax number is (516) 756-5114.

Sincerely,
Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

VC:pj

RECEIVED
JAN 21 1999

ALTANA

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

December 9, 1998

NEW CORRESP
NC to FA

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 2, Room 286
7500 Standish Place
Rockville, MD. 20855-2773

**RE: ANDA 75-391 FACSIMILE AMENDMENT**
**Clobetasol Propionate Topical Solution USP, 0.05%**

Dear Dr. Patel:

Reference is made to our original Abbreviated New Drug Application of May 27, 1998, as well as your telefax of November 23, 1998 in which several deficiencies were noted.

We wish to respond to each of the concerns noted in your November 23, 1998 telefax as follows:

**A. Deficiencies**

1. Comment:
Please justify the excess of active, Clobetasol Propionate, USP in the drug product.

Response:
Upon review of the testing data we find that the overage of the active ingredient cannot be justified. The formulas have therefore, been revised to eliminate the excess. Copies of the new formulas are presented in Attachment 1.

2. Comment:
Please state the function of the Carbomer 934P, NF in the drug product formulation.

Response:
Carbomer 934P, NF is included in the formula because Glaxo's Temovate contains it. The function of carbomers in topical steroid solutions is to provide slight thickening of the solution.

3. Comment:
Please revise the drug substance tests and specifications to include residual solvent testing.

Response:
The drug substance tests and specifications have been revised to include residual solvent testing. Please see revised specifications in Attachment 2. Revised procedures may be found in Attachment 3. Analytical results for residual solvent testing for lot 9612000143 (lot used in the exhibit batch) are located in Attachment 4.

Please note we will be utilizing as an alternate contract listing laboratory for OVI and residual solvent testing. A copy of a letter indicating their adherence to cGMP's is included in Attachment 5.

4. Comment:
You have stated that your product will be filled within six (6) weeks from the date of manufacture. Please identify the testing that will be performed on batches held for more than 30 days.

Response:
Full in-process testing is repeated if the product is held more than 30 days. The SOP is being revised to include this time frame.

5. Comment:
In Step of the manufacturing process, in-process samples are taken, and in Step the batch is strained into containers. Please explain the straining before sampling, and what effect straining may have on the product.

Response:
Sampling of the exhibition batch, lot number A301, was performed using which requires that samples be taken during transfer to the storage containers; i.e. post straining. This was documented in the batch record folder. An additional copy of this documentation is presented in Attachment 6.

The strainer is composed of stainless steel and will have no effect on the product other than to remove any inadvertent gross physical contaminants.

6. Comment:
Please set RSD limits for in-process testing for clobetasol propionate and isopropyl alcohol assays.

Response:
RSD limits have been set for the clobetasol propionate and isopropyl alcohol assays. Please see revised in-process specifications located in Attachment 7.

7. Comment:
Please revise the stability tests and specification to:

a. reduce the individual and total degradation products specification, based upon data submitted.

b. reduce the weight loss specification.

Response:
The stability specifications have been revised to reduce the individual and total degradation products, and the weight loss specification. Please see revised specifications in Attachment 8.

8. Comment:
Please describe the cycling conditions for the cycling stability study.

Response:
The product was put through four cycles. Each cycle consisted of one week at 4°C followed by two days at 40°C. Future cycling studies will be conducted using these parameters.

Subsequent to this cycling study, our stability SOP was revised on the recommendation of Dr. Paul Schwartz to use three cycles, with each cycle consisting of two days at 4°C followed by two days at 40°C. Future cycling studies will be conducted using these parameters.

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

As requested:

Altana Inc. acknowledges that the firms referenced in our application must be in compliance with cGMP at the time of approval.

Updated stability data may be found in Attachment 9.

**Labeling Deficiencies**:

1. GENERAL COMMENT:

   Since this product is a subject of a USP monograph which initiated storage recommendations, we recommend that you revise all labeling to be in accord with USP:

   > Store at controlled room temperature, 15 - 30 C (59 -86 F). Do not refrigerate. Do not use near an open flame.

   Response:
   All container, carton and insert labeling have been revised as suggested.

2. Comment:
   Container (25 mL and 50 mL)

   a. See GENERAL COMMENT.

   b. Revise to include on the front panel, FOR USE ON THE SCALP

   c. Revise the "Each mL contains" statement to read, CONTAINS: Clobetasol propionate 0.05% (0.5 mg/g) in a .....

   Response:
   Revised container labeling which incorporates the Agency's suggestions is included in Attachment 10

3. Comment:

   CARTON (25 mL and 50 mL)

   See CONTAINER comments.
   Response:
   Revised carton labeling may be found in Attachment 11.

4. Comment:

   a. DESCRIPTION

      i. Revise the chemical name to the second listed in the official monograph for the clobetasol propionate in the USP 23, supplement #2.

ii. Revise the first sentence in the third paragraph to read, ...molecular formula, molecular weight of 466.98.

iii. Revise the first sentence of the fourth paragraph to read:
Clobetasol propionate...contains: 0.5 mg/g clobetasol propionate in a ...

b. CONTRAINDICATIONS

Revise so that the second "inpatients" appears as two words, "in patients".

c. ADVERSE REACTONS

Revise the second paragraph to read,
..sensation, which occurred in approximately 10% of the patients; scalp pustules, which occurred in approximately 1% of the patients; and tingling and folliculitis, each of which occurred in 0.7% of the patients. Less...and eye irritation.

d. OVERDOSAGE

Revise to read,
Topically applied clobetasol propionate solution can be...

e. HOW SUPPLIES

See GENERAL COMMENT.

Revised insert labeling which incorporates all of the Agency's recommendations may be found in Attachment 12.

A side by side comparison of our revised labeling with that of our last submission is included as follows:

| | | |
|---|---|---|
| Container | - | Attachment 13 |
| Carton | - | Attachment 14 |
| Insert | - | Attachment 15 |

We also note that the Agency reserves 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 also acknowledge that the bioequivalency comments provided in your November 23 correspondence are preliminary and may be revised as a result of the review of the entire application. We are aware that additional data may be required.

Please note that a field copy of this amendment has been submitted to the local district office.

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

Sincerely,
Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

VC:isf

Attachments

ALTANA

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

**Federal Express**

505(b)1 OK 6/16/98



May 27, 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

**Original Submission**
**Abbreviated New Drug Application**
**Clobetasol Propionate Topical Solution USP, 0.05%**

Dear Sir or Madam:

In accordance with the regulations set forth in 21 CFR 314.94 and Section 505(j) of the Federal Food, Drug, and Cosmetic Act, Altana Inc. is submitting this Abbreviated New Drug Application to market a new drug, Clobetasol Propionate Topical Solution USP, 0.05%.

The reference listed drug which is the basis for this submission is Temovate® (clobetasol propionate) Scalp Application 0.05% (NDA 19-966), manufactured by Glaxo. The proposed drug, Clobetasol Propionate Topical Solution USP, 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 (#A301) included in this application was fully packaged utilizing both the 25 mL and 50 mL 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 two (2) volume submission, along with Form FDA 356h, is the required Patent Certification and Exclusivity statements, draft Labeling, request for Bioequivalence Waiver, 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 and 1.2 and a copy of the Methods Validation package) is being sent to the New York District Office under separate cover.

If you require any additional information please contact me at (516) 454-7677 extension 2091.

Sincerely,

Altana Inc.

Virginia Carman

Virginia Carman
*Associate Director*, Regulatory Affairs

Enclosures

VC/ab

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