CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-502

CHEMISTRY REVIEW(S)

L. Golson

MAY 17 2001

38. Chemistry Comments to be provided to the Applicant:

ANDA: 75-502 APPLICANT: Altana Inc.

DRUG PRODUCT: Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05% (base)

The deficiencies presented below represent FAX deficiencies.

A. Deficiencies:

1. Please tighten the stability specifications regarding betamethasone degradation product and identify the peak at RRT 0.50 and provide limits for it.

2. Since the cycle study could not be performed using 45 C as the high temperature, please provide test results for a cycle study using 40° C instead.

3. Please be informed that the reduced testing stability protocol requires prior approval.

4. Please tighten your limit for pH for in-process, release and stability.

5. Please tighten the raw material, release and stability specifications regarding clotrimazole for other individual related substances based on your data.

Sincerely yours,

Paul Schwartz for

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

JUL 3 2000

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ANDA: 75-502 APPLICANT: Altana Inc.

DRUG PRODUCT: Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05% (base)

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. remains 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 new DMF deficiencies have been addressed.

2. Please revise your specifications for Clotrimazole drug substance manufactured by egarding the residual solvent ppm and a provide a certificate of analysis to show it complies.

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

4. Please tighten your specifications for in-process and finished product regarding betamethasone dipropionate impurities and related compounds.

5. Please provide the test results for the cycle study.

6. Please revise your limits based on your stability data regarding the betamethasone degradation products.

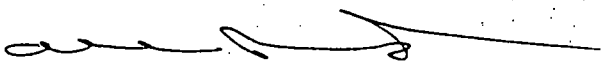
7. Please revise your specification for finished drug product and stability regarding the microbial limits to include Escherichia coli and Salmonella species and total microbial count.

8. Please provide limit of detection and limit of quantitation for degradation products for your method validation for clotrimazole and betamethasone dipropionate cream.

9. Please explain why your certificates of analysis for the cream list size 15 g and 45 g tube; each tube size should have its own certificate of analysis. In addition, your certificate of analysis did not provide results for betamethasone degradation products and total microbial limits.

10. We have not received your response to the communication from the Division of Bioequivalence dated 12/27/99.

Sincerely yours,



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

MAY - 3 1999

38. Chemistry Comments to be provided to the Applicant:

ANDA: 75-502 APPLICANT: Altana Inc.

DRUG PRODUCT: Clotrimazole and Betamethasone Dipropionate Cream USP, 1%/0.05% (base)

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please revise your certificate of analysis for clotrimazole to include test procedure and limits for others impurities and related substances, residual solvents and particle size.

2. Please revise your certificates of analysis on p. 2278 and p. 2301 to include test results for all tests.

3. Please revise your specifications for in-process controls to include test procedure and limits for blend uniformity analysis.

4. Please revise your specifications for the finished drug product to include test procedure and limits for both the individual and total impurities and related compounds.

5. Based on your stability data regarding the degradation products, please revise your limits.

6. Please provide the test results for the cycle study and explain why the description test failed.

7. The are deficient. The DMF's holders have been notified.

8. Please revise the specifications for finished drug product to include the mean specifications and limits for homogeneity test.

9. Please revise your stability specifications to tighten the viscosity limits.

10. Please revise your stability specifications to include specification for the mean of the homogeneity test.

11. Please revise your stability specifications to tighten your limits for weight loss test.

12. Please revise your formulation to indicate that the component is Cetostearyl Alcohol

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 the approval.

2. Your bioequivalence study is under review.

Sincerely yours,

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

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 75-502

3. NAME AND ADDRESS OF APPLICANT

Altana Inc.
60 Baylis Road
Melville, NY 11747

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that, in the opinion of the applicant and to the best of the applicant's knowledge, patent # 4298604 Claimed the reference listed drug Lotrisone Cream, manufactured by Schering Corporation, will expire on October 6, 2000.

The firm certifies that there is no period of marketing exclusivity for the reference listed drug Lotrisone Cream.

5. SUPPLEMENT(s)

Original 11/11/98

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Clotrimazole and Betamethasone Dipropionate

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

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 1/7/00
Amendment 11/10/00
Amendment 4/11/01 (Gratuitous)
Amendment 5/23/01
Amendment 5/24/01
Amendment 5/29/01
Amendment 6/1/01

10. PHARMACOLOGICAL CATEGORY

For treatment of dermal infections

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

10713

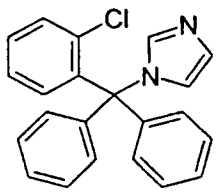
13. DOSAGE FORM

14. POTENCY

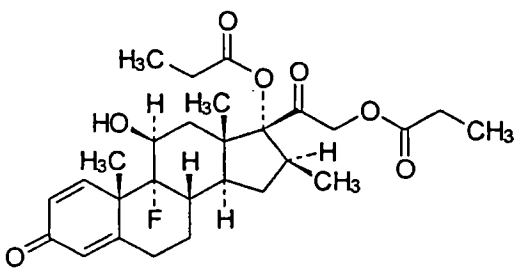
Cream 1%/0.05% (base)

15. CHEMICAL NAME AND STRUCTURE

Generic name: Clotrimazole
Chemical name: 1*H*-Imidazole, 1-[(2-chlorophenyl)diphenylmethyl]-
Chemical formula: $C_{22}H_{17}ClN_2$
Molecular weight: 344.85
CAS number: 23593-75-1
Chemical structure:



Generic name: Betamethasone Dipropionate
Chemical name: Pregna-1,4-diene-3,20-dione, 9-fluoro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, (11β,16β)-
Chemical formula: $C_{28}H_{37}FO_7$
Molecular weight: 504.6
CAS number: 5593-20-4
Chemical structure:



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable .

19. REVIEWER: DATE COMPLETED:

N. Nashed 6/4/01

Nashed E. Nashed, Ph.D. 6/4/01

Supervisor: Paul Schwartz, Ph.D. 5/30/01 & 6/4/01

P J 6/4/01

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

Chem Rev 4

6/4/01