

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76075

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION **CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW**

1. CHEMIST'S REVIEW NUMBER

1

2. ANDA NUMBER

76-075

3. NAME AND ADDRESS OF APPLICANT

Altana Inc.

Attention: Virginia Carman

60 Baylis Road

Melville, NY 11747

Telephone: 631-454-7677 ext. 2091

Fax: 631-756-5114

4. LEGAL BASIS for ANDA SUBMISSION

The basis of Altana's proposed ANDA for Econazole Nitrate Cream, 1% is the reference listed drug, Spectazole Cream (econazole nitrate 1%), manufactured by Ortho Pharmaceutical Corporation, a Johnson & Johnson Company, NDA 18-751. According to the information published in the list of Approved Drug Products 20th Ed, there is no unexpired exclusivity for the reference listed drug. The applicant certifies that all the listed patents claimed in the United States for the listed drug product have expired. The proposed drug has the same strength, dosage form, indications, route of administration, qualitative and quantitative composition with regards to active and inactive ingredients as those of the listed reference drug (v 1.1, pp12-16).

5. SUPPLEMENT(s)

None

6. NAME OF DRUG

Econazole Nitrate Cream, 1%

7. NONPROPRIETARY NAME

Econazole Nitrate Cream, 1%

8. SUPPLEMENT(s) PROVIDE(s) FOR

None

9. AMENDMENTS AND OTHER DATES

December 22, 2000

Original submission

10. PHARMACOLOGICAL CATEGORY

Antifungal agent

11. HOW DISPENSED

Prescription

12. RELATED IND/NDA/DMF(s)

Econazole nitrate		V 1.5, p 1335
Aluminum tubes (15 g, 30 g, and 90 g) blind end tubes		V 1.6 p1824
tube liner		V 1.6, p 1834?
Aluminum tubes (90 g).		V 1.6, p1628
#16 Fez pucture tip		V 1.6, p1836
Aluminum tubes 85 g.		V 1.6, p1828
Pointed fez caps	resin for	V 1.6, p1832

13. DOSAGE FORM

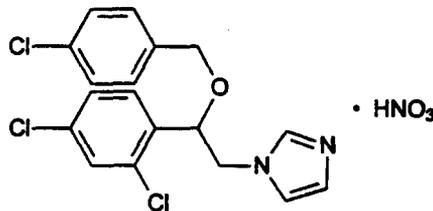
Cream

14. POTENCY

1%

15. CHEMICAL NAME AND STRUCTURE

Econazole Nitrate. 1H-Imidazole, 1-[2-[(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-, mononitrate, (\pm)-.C₁₈H₁₅Cl₃N₂O•HNO₃. 444.7. 68797-31-9. Antifungal.



16. RECORDS AND REPORTS

None

17. COMMENTS

The following sections are not satisfactory: Synthesis, Raw Material Controls, Stability, Container/Closure, laboratory Controls, and Stability. The bioequivalency and labeling reviews are pending. The overall establishment inspection results are also pending.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable [MINOR AMENDMENT].

19. REVIEWER AND DATE COMPLETED

Ramesh Sood/April 24, 2001

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Chem-Review #1

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION **CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW**

1. CHEMIST'S REVIEW NUMBER

2

2. ANDA NUMBER

76-075

3. NAME AND ADDRESS OF APPLICANT

Altana Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747
Telephone: 631-454-7677 ext. 2091 Fax: 631-756-5114

4. LEGAL BASIS for ANDA SUBMISSION

The basis of Altana's proposed ANDA for Econazole Nitrate Cream, 1% is the reference listed drug, Spectazole Cream (econazole nitrate 1%), manufactured by Ortho Pharmaceutical Corporation, a Johnson & Johnson Company, NDA 18-751. According to the information published in the list of Approved Drug Products 20th Ed, there is no unexpired exclusivity for the reference listed drug. The applicant certifies that all the listed patents claimed in the United States for the listed drug product have expired. The proposed drug has the same strength, dosage form, indications, route of administration, qualitative and quantitative composition with regards to active and inactive ingredients as those of the listed reference drug (v 1.1, pp12-16).

5. SUPPLEMENT(s)

None

6. NAME OF DRUG

Econazole Nitrate Cream, 1%

7. NONPROPRIETARY NAME

Econazole Nitrate Cream, 1%

8. SUPPLEMENT(s) PROVIDE(s) FOR

None

9. AMENDMENTS AND OTHER DATES

December 22, 2000 Original submission
August 13, 2001 Minor Amendment

10. PHARMACOLOGICAL CATEGORY

Antifungal agent

11. HOW DISPENSED

Prescription

12. RELATED IND/NDA/DMF(s)

Product	Holder	DMF No.	LOA
Econazole nitrate			V 1.5, p 1335
Aluminum tubes (15 g, 30 g, and 90 g) blind end tubes			V 1.6 p1824
tube liner			V 1.6, p 1834?
Aluminum tubes (90 g).			V 1.6, p1626
#16 Fez pucture tip			V 1.6, p1836
Aluminum tubes 85 g.			V 1.6, p1828
resin for			
Pointed fez caps			V 1.6, p1832

13. DOSAGE FORM

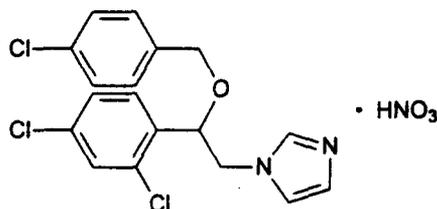
Cream

14. POTENCY

1%

15. CHEMICAL NAME AND STRUCTURE

Econazole Nitrate. 1*H*-Imidazole, 1-[2-[(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-, mononitrate, (±)-.C₁₈H₁₅Cl₃N₂O•HNO₃.
444.7. 68797-31-9. Antifungal.

**16. RECORDS AND REPORTS**

None

17. COMMENTS

The applicant has responded to most of the deficiencies from review #1 satisfactorily, however, the synthesis (particularly DMF container, laboratory controls and stability sections remain deficient. The bioequivalency and labeling reviews are pending. The overall establishment inspection results and method validation results are acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable [MINOR AMENDMENT].

19. REVIEWER AND DATE COMPLETED

Ramesh Sood/August 21, 2001

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Chem Review # 2

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION **CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW**

1. CHEMIST'S REVIEW NUMBER

3

2. ANDA NUMBER

76-075

3. NAME AND ADDRESS OF APPLICANT

Altana Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747
Telephone: 631-454-7677 ext. 2091 Fax: 631-756-5114

4. LEGAL BASIS for ANDA SUBMISSION

The basis of Altana's proposed ANDA for Econazole Nitrate Cream, 1% is the reference listed drug, Spectazole Cream (econazole nitrate 1%), manufactured by Ortho Pharmaceutical Corporation, a Johnson & Johnson Company, NDA 18-751. According to the information published in the list of Approved Drug Products 20th Ed, there is no unexpired exclusivity for the reference listed drug. The applicant certifies that all the listed patents claimed in the United States for the listed drug product have expired. The proposed drug has the same strength, dosage form, indications, route of administration, qualitative and quantitative composition with regards to active and inactive ingredients as those of the listed reference drug (v 1.1, pp12-16).

5. SUPPLEMENT(s)

None

6. NAME OF DRUG

Econazole Nitrate Cream, 1%

7. NONPROPRIETARY NAME

Econazole Nitrate Cream, 1%

8. SUPPLEMENT(s) PROVIDE(s) FOR

None

9. AMENDMENTS AND OTHER DATES

December 22, 2000	Original submission
August 13, 2001	Minor amendment
September 5, 2001	Deficiency letter based on review #2
June 25, 2002	Minor amendment

10. PHARMACOLOGICAL CATEGORY

Antifungal agent

11. HOW DISPENSED

Prescription

12. RELATED IND/NDA/DMF(s)

Econazole nitrate			V 1.5, p 1335
Aluminum tubes (15 g, 30 g, and 90 g) blind end tubes			V 1.6 p1824
tube liner			V 1.6, p1834?
Aluminum tubes (90 g).			V 1.6, p1828
#16 Fez pucture tip			V 1.6, p1836
Aluminum tubes 85 g.			V 1.6, p1828
Pointed fez caps	resin for		V 1.6, p1832

13. DOSAGE FORM

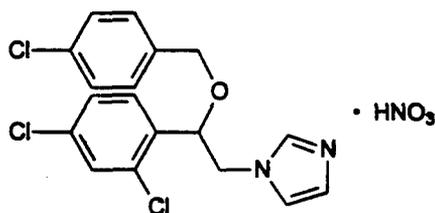
Cream

14. POTENCY

1%

15. CHEMICAL NAME AND STRUCTURE

Econazole Nitrate. 1*H*-Imidazole, 1-[2-[(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-, mononitrate, (\pm)-.C₁₈H₁₅Cl₃N₂O•HNO₃.
444.7. 68797-31-9. Antifungal.

**16. RECORDS AND REPORTS**

None

17. COMMENTS

The synthesis (DMF laboratory controls and stability sections remain deficient. The bioequivalency review is still pending. The overall establishment inspection results and method validation results are acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable [MINOR AMENDMENT].

19. REVIEWER AND DATE COMPLETED

Gil Kang/August 9, 2002

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Chem Review #3

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER

4

2. ANDA NUMBER

76-075

3. NAME AND ADDRESS OF APPLICANT

Altana Inc.

Attention: Virginia Carman

60 Baylis Road

Melville, NY 11747

Telephone: 631-454-7677 ext. 2091

Fax: 631-756-5114

4. LEGAL BASIS for ANDA SUBMISSION

The basis of Altana's proposed ANDA for Econazole Nitrate Cream, 1% is the reference listed drug, Spectazole Cream (econazole nitrate 1%), manufactured by Ortho Pharmaceutical Corporation, a Johnson & Johnson Company, NDA 18-751. According to the information published in the list of Approved Drug Products 20th Ed, there is no unexpired exclusivity for the reference listed drug.

5. SUPPLEMENT(s)

None

6. NAME OF DRUG

Econazole Nitrate Cream, 1%

7. NONPROPRIETARY NAME

Econazole Nitrate Cream, 1%

8. SUPPLEMENT(s) PROVIDE(s) FOR

None

9. AMENDMENTS AND OTHER DATES

December 22, 2000

Original submission

August 13, 2001

Minor amendment

September 5, 2001

Deficiency letter based on review #2

June 25, 2002

Minor amendment

August 28, 2002

Deficiency letter based on review #3

September 17, 2002

Minor amendment

October 21, 2002

Telephone amendment

November 6, 2002

Telephone amendment

10. PHARMACOLOGICAL CATEGORY

Antifungal agent

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Chem-Review #4

JUN - 8 2001

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-075

APPLICANT: Altana Inc.

DRUG PRODUCT: Econazole Nitrate Cream, 1%

The deficiencies presented below represent **MINOR** deficiencies.

A. Deficiencies:

1. The DMF# Econazole Nitrate USP, is currently inadequate. The DMF holder, has been notified. Please ensure that there has been a response submitted by the DMF Holder.
2. Please give the time period after which raw materials benzoic acid and butylated hydroxyanisole will be re-tested as per your retest schedule.
3. Please provide the DMF information (DMF # and letter of authorization) on the caps for 85 g tubes prepared from resin by
4. Please provide liner integrity testing results for all tube sizes. The data provided on page 1870 of your application for the are too old. Please provide recent test results for the tube liner
5. Please provide dimensional drawings for 85 g tubes from
6. Please tighten your specification for the total aerobic microbial count and include release and stability specifications for the total yeast and mold count.
7. Please tighten your specification for total and individual impurity/degradant in release and stability protocols based on the observed values from your product and the values from the innovator's product at or near expiry after storage at room temperature.
8. Please include a preservative effectiveness test to be performed at time zero and expiration date to justify

the proposed specification of % for benzoic acid.

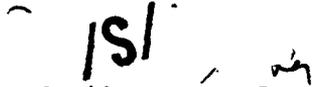
9. The container system mentioned in the stability results for 15 g on pages 2328-2331 (described as is not consistent with the container system described on page 1798 and other places (described as manufactured by . Please explain the inconsistency. Please also confirm that the listed as manufacturer of the 90 g in stability reports and are in fact the same entity.
10. (lot # 9803000144) as the supplier of drug substance according to stability summary sheets is inconsistent with as the supplier for the drug substance according to batch records. Please clarify and revise.
11. Please tighten your viscosity release and stability specifications based on the observed values of the exhibit batch.
12. Please add quantitative specification for butylated hydroxyanisole in your release and stability protocols.
13. Implementation of the post approval reduced testing program for the stability studies requires prior approval supplement supported by appropriate data.

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

1. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.
2. Your labeling information is pending review. Deficiencies, if any, will be communicated separately.
3. All facilities referenced in the ANDA must have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the office of compliance.

4. We require an acceptable methods validation on the drug product to support the ANDA and are currently scheduling the study with the District Laboratory. Please provide samples promptly when contacted. Please also provide a commitment to work with us to expeditiously resolve any deficiencies from the methods validation study if the ANDA is approved prior to its completion.
5. Please provide all available long-term stability data to update your studies.

Sincerely yours,


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

SEP -5 2001

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-075

APPLICANT: Altana Inc.

DRUG PRODUCT: Econazole Nitrate Cream, 1%

The deficiencies presented below represent **MINOR** deficiencies.

A. Deficiencies:

1. The DMF# Econazole Nitrate USP, is currently inadequate. The DMF holder, has been notified. Please do not submit a MINOR amendment until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the agency.
2. You have failed to demonstrate the liner integrity of packaging tubes in your amendment dated August 13, 2001. Please provide the liner integrity test results for all tube sizes to demonstrate that there are no voids/bare metal exposure areas in the containers.
3. Your proposed release and stability specifications for total impurities and stability specification for the individual impurity are still not acceptable. Since the full-term stability data of your product show that the product is stable, please tighten your release and stability specifications for total impurities and stability specifications for individual impurities.
4. Please provide data to support the effectiveness of benzoic acid as effective microbial preservative at the proposed lower limit of %.
5. The method currently used for butylated hydroxyanisole (BHA) is a qualitative method. Please submit the modified test method and the validation data to show that the method is adequate for determining the amount of BHA at release and expiry. The proposed lower limit for BHA contents should be supported by the data

showing the effectiveness of BHA at the proposed level.

6. The release specification of NLT % of label claim for BHA is not acceptable. Please set a range for BHA in line with the initial formulation.

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

1. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.
2. Your labeling information is pending review. Deficiencies, if any, will be communicated separately.

Sincerely yours,

RS

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

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 76075/000**
Stamp: **26-DEC-2000** Regulatory Due:
Applicant: **ALTANA**
60 BAYLIS RD
MELVILLE, NY 11747

Priority:
Action Goal:
Brand Name:
Established Name: **ECONAZOLE NITRATE**
Generic Name:
Dosage Form: **CRM (CREAM)**
Strength: **1 %**

Org Code: **600**District Goal: **26-NOV-2001**

FDA Contacts: **E. HU (HFD-42)**
P. SCHWARTZ (HFD-629)

301-827-2828 , Project Manager
301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 10-MAY-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **2410271**
ALTANA INC
CANTIAGUE ROCK RD
HICKSVILLE, NY 11802

DMF No:
AADA No:

Profile: **OIN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **10-MAY-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE
MANUFACTURER**

Establishment: **2432435**
ALTANA INC
60 BAYLIS RD
MELVILLE, NY 11747

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-JAN-2001**
Decision: **ACCEPTABLE**
Reason:

Responsibilities: **DRUG SUBSTANCE STABILITY
TESTER**

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-JAN-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**