CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76005

CHEMISTRY REVIEW(S)

APPROVAL PACKAGE SUMMARY FOR 76-005

ANDA: 76-005

FIRM: Taro Pharmaceuticals USA, Inc.

DRUG: Econazole Nitrate

DOSAGE: Cream

STRENGTH: 1%

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 10/29/02

BIO STUDY/BIOEQUIVALENCE: Bio is acceptable 9/13/02

METHOD VALIDATION: Method Validation is acceptable 7/19/01

STABILITY: The firm has provided satisfactory 3 months accelerated stability data at 40°C/75%RH and 24 months room temperature stability data at 25±2°C/60±5%RH for the biobatch (L) S123-51820 and 12 months room temperature stability data for the second batch (L) S123-5234 for all packaging sizes.

LABELING REVIEW STATUS: Labeling is satisfactory 12/27/01

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has provided the master formula and batch record for intended production for kg. Also, submitted a copy of the executed batch record lot #S123-51820 for kg.
The firm will be using the same drug substance manufacturer, same equipment and same process.

COMMENTS: The application is approvable.

/S/ 11/12/02

REVIEWER: Nashed E. Nashed, Ph.D. DATE: 11/12/02

SUPERVISOR: James M. Fan 11/14/02

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW #** **No. 1**

2. **ANDA #** 76-005 **[Econazole Nitrate Cream, 1%]**

3. **NAME AND ADDRESS OF APPLICANT:**
Taro Pharmaceuticals USA, Inc.
Attention: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532
Telephone: (914) 345-9001 FAX: (914) 345-8728

4. **LEGAL BASIS OF SUBMISSION:**
This ANDA for Econazole Nitrate Cream, 1% is based on the reference listed drug: Spectrazole® (econazole nitrate) 1% Cream, manufactured by: DERMATOLOGICAL DIVISION, ORTHO PHARMACEUTICAL CORPORATION, Rartitan, New Jersey 08869, a *Johnson-Johnson* company. An ANDA suitability petition was not required since the proposed drug product has the same strength, dosage form, route of administration and has the same indications as the listed drug. There are no unexpired patents and no exclusivities for the reference listed drug (see p. 6 for certifications, dated 09/113/01).

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Econazole Nitrate Cream, 1%

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**
Taro:
10/10/00 Original submission (receive on 10/11/00)
11/21/00 Amendment (response to telephone request from FDA)

FDA:
11/16/00 Telephone request (from Paras Patel of FDA)
11/30/00 Date of acknowledgment letter (acceptable for filing on 10/11/00)

10. **PHARMACOLOGICAL CATEGORY:**
Antifungal agent

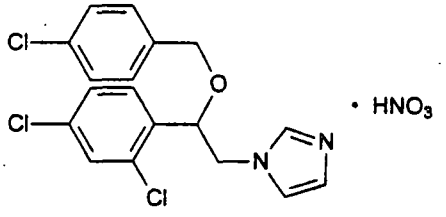
11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**
NDA: 18-751 [Spectrazole® (econazole nitrate) 1% Cream, *Johnson-Johnson*]
The NDA was approved on 12/23/1982.
(See Item 37 for DMF list and comments).

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, (±)-.$C_{18}H_{15}Cl_3N_2O \cdot HNO_3$. 444.7. 68797-31-9. Antifungal.



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:
The drug substance, Econazole Nitrate, is listed in USP 24 (pp. 621-622). The drug product, Econazole Nitrate Cream is not a subject of the USP monograph as of the review. DMF of the drug substance is inadequate. There are many CMC deficiencies.

Labeling review and bioequivalence review are pending. No microbiological review is needed.

Acceptable EER has not been received.

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Not approvable (MINOR amendment)

19. **REVIEWER**: Shing H. Liu, Ph.D. **DATE COMPLETED**: 02/15/01
Revised 02/20/01

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Chem Review #1

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW #** **No. 2**

2. **ANDA #** 76-005 [**Econazole Nitrate Cream, 1%**]

3. **NAME AND ADDRESS OF APPLICANT:**
Taro Pharmaceuticals USA, Inc.
Attention: Kalpana Rao
5 Skyline Drive, Hawthorne, NY 10532

4. **LEGAL BASIS OF SUBMISSION:** See CR #1

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Econazole Nitrate Cream, 1%

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**
* denotes the submission(s) reviewed in the chemistry review #2

Taro:

10/10/00	Original submission (receive on 10/11/00)
11/21/00	Amendment (response to telephone request from FDA)
06/22/01	*Telephone amendment (Re: bioequivalence)
08/20/01	*MINOR amendment (response to NA letter of 03/09/01)
10/02/01	*Amendment (bio)
12/06/01	*Amendment (labeling)
01/25/02	*Amendment (bio)
02/08/02	*Amendment (bio)

FDA:

11/16/00	Telephone request (from Paras Patel of FDA)
11/30/00	Acknowledgment letter (acceptable for filing on 10/11/00)
03/09/01	NA (MINOR) letter (based on CR #1)

10. **PHARMACOLOGICAL CATEGORY:** Antifungal agent

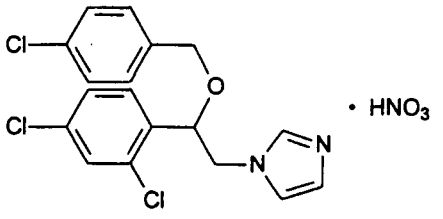
11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):** See CR #1

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, (±)-.$C_{18}H_{15}Cl_3N_2O \cdot HNO_3$. 444.7. 68797-31-9. Antifungal.



16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**
The drug substance, Econazole Nitrate, is listed in USP 24 (pp. 621-622). The drug product, Econazole Nitrate Cream is not a subject of the USP monograph as of the review. DMF of the drug substance is deficient. All except one of the applicant's responses to the CMC deficiencies cited in the last NA letter are acceptable.

Method validation was performed by Northeast Regional Laboratory. The validation report (dated 07/19/01) concluded that the applicant's method appears to be suitable for regulatory analysis of this product.

Labeling approval summary was signed off on 12/27/01. Taro's response to bio deficiencies is under review as of 02/19/02. No microbiological review is needed.

Acceptable EER was received on 11/28/01.

The firm has provided satisfactory acknowledgment and response (regarding submission of accrued stability data) for the comments conveyed to them under Section B of the last NA letter.

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Not Approvable (MINOR amendment)

19. **REVIEWER:** Shing H. Liu, Ph.D. **DATE COMPLETED:** 09/28/01
Revised on 01/17/02 after bio review was received by chemistry project manager
Revised again on 02/06/02 after recent amendment of Type II DMF was reviewed.
Revised again after 02/08/02 bio amendment was received.

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Chem - Review #2

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **CHEMIST'S REVIEW #** No. 3

2. **ANDA #** 76-005

3. **NAME AND ADDRESS OF APPLICANT:**

   Taro Pharmaceuticals USA, Inc.
   5 Skyline Drive
   Hawthorne, NY 10532

4. **LEGAL BASIS OF SUBMISSION:** See CR #1

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Econazole Nitrate Cream, 1%

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

   * denotes the submission(s) reviewed in the chemistry review #2

   Taro:

10/10/00	Original submission (receive on 10/11/00)
11/21/00	Amendment (response to telephone request from FDA)
06/22/01	*Telephone amendment (Re: bioequivalence)
08/20/01	*MINOR amendment (response to NA letter of 03/09/01)
10/02/01	*Amendment (bio)
12/06/01	*Amendment (labeling)
01/25/02	*Amendment (bio)
02/08/02	*Amendment (bio)
6/7/02	Minor Amendment
9/13/02	Minor Amendment
11/6/02	Telephone Amendment
11/13/02	Telephone Amendment

   FDA:

11/16/00	Telephone request (from Paras Patel of FDA)
11/30/00	Acknowledgment letter (acceptable for filing on 10/11/00)
03/09/01	NA (MINOR) letter (based on CR #1)

10. **PHARMACOLOGICAL CATEGORY:** Antifungal agent

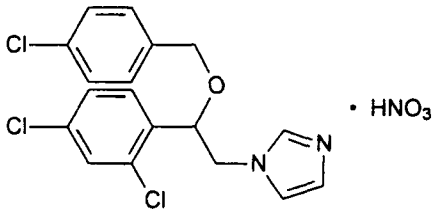
11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):** See CR #1

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, (±)-.$C_{18}H_{15}Cl_3N_2O \cdot HNO_3$. 444.7. 68797-31-9. Antifungal.



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:
None

18. **CONCLUSIONS AND RECOMMENDATIONS**:

The application is approvable.

19. **REVIEWER**:

/S/ 11/14/02
Nashed E. Nashed, Ph.D. Date: 11/12/02

Supervisor: James M. Fan

cc: ANDA 76-005
Division File
Field Copy

Endorsements:
HFD-627/N. Nashed 11/14/02
HFD-627/J. Fan 11/14/02

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Chem Review #3

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38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-005 APPLICANT: Taro Pharmaceuticals USA Inc.

DRUG PRODUCT: Econazole Nitrate Cream, 1%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File No. is deficient. The holder of the DMF, has been notified of the DMF deficiencies. Please do not respond to this letter until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the Agency.

2. Please justify the proposed limits for the individual unknown and total degradants in the finished product release and stability. Please also establish the limit for individual known degradant(s), unless you can prove that there are no known degradants.

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

Your response to the bioequivalence deficiencies is under review. Comments, if any, will be communicated to you under a separate cover.

Sincerely yours,

/S/

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

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-005 **APPLICANT:** Taro Pharmaceuticals USA Inc.

DRUG PRODUCT: Econazole Nitrate Cream, 1%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File No. is deficient. The holder of the DMF, has been notified of the DMF deficiencies. 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. Please separate the individual impurities into known and unknown impurities, and set appropriate limits for the drug substance. Known impurities should be identified. If the manufacturer does not use Organic Volatile Impurities (OVIs) in the manufacture of Econazole Nitrate, such a certification statement should be included in your specification sheet.

3. You should revise your proposed specifications for particle size to include The limits should be established to be close to the observed values for lot #8358-R, which was used in the bio batch.

4. Please establish specifications for Residual Solvents based on the current manufacturer's Certificate of Analysis (COA), and provide test results for lot #8358-R based on a validated analytical method. A validation report should be submitted.

5. Please provide blank batch records for filling and packaging, which are missing in the submission.

6. Regarding your in-process specifications, please establish limits for homogeneity and viscosity. RSD for test should be $\leq$ %.

7. Please specify the maximum holding time for the bulk before packaging.

8. Please establish specifications for degradation products, viscosity and homogeneity in your finished product specifications. Known impurities should be included in the specifications.

9. Please explain why is included under Benzoic Acid Assay on page 1206.

10. Please establish specifications for degradation products, viscosity and homogeneity in your stability specifications.

11. Please add a preservative effectiveness test to the stability specifications. This test should be performed at time zero and just prior to the proposed expiration date.

12. Regarding the(test in the stability specifications, the RSD value of NMT % should be tightened.

13. Please add a test for Butylated Hydroxytoluene (BHT) assay in the stability test protocol and establish a specification.

14. Please clarify whether you intend to include total yeast and Mold count under the total aerobic count.

15. Please provide the missing pages of the three-page Preservative Challenge Test report (see p. 1285). Only the first page of the report is found in the ANDA.

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 ANDA must be in compliance with cGMPs at the time of approval.

2. Please submit all available room temperature stability data.

3. The bioequivalence information, which you have provided, is under review. Comments will be communicated to you under a separate cover.

4. The labeling information, which you have provided, is under review. Comments will be communicated to you under a separate cover.

5. The acceptance of your proposed 24 month expiration dating period is contingent upon you providing the requested stability specifications.

6. Please be advised that in the event of regulatory dispute, the USP methods for Econazole Nitrate USP will prevail.

7. We requested the Northeast Regional Laboratory to conduct method validation on your finished product. Please provide samples when requested.

Sincerely yours,

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