CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-387

CHEMISTRY REVIEW(S)

ANDA 76-387

Clotrimazole Troche, 10 mg

Roxane Laboratories, Inc.

Ramesh Sood, Ph.D.
Division 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-387 (First Generic)

2. REVIEW #: 1

3. REVIEW DATE: June 28, 2002

4. REVIEWER: Ramesh Sood, Ph.D

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	Mar 28, 2002
New Correspondence	May 20, 2002

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc.

Address: 1809 Wilson Road, Columbus, OH 43228

Representative: Elizabeth Ernst

Telephone: 614-272-4785

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Clotrimazole Troche

9. LEGAL BASIS FOR SUBMISSION: The basis for this ANDA is Bayer Corporations's Mycelex (clotrimazole) Troche, 10 mg (NDA 18713). The firm also states that, in its opinion, there are no unexpired patents or marketing exclusivity indicated for the RLD.

10. PHARMACOL. CATEGORY: Local treatment of oropharygeal candidiasis.

11. DOSAGE FORM: Troche

12. STRENGTH/POTENCY: 10 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: x___Rx ___OTC

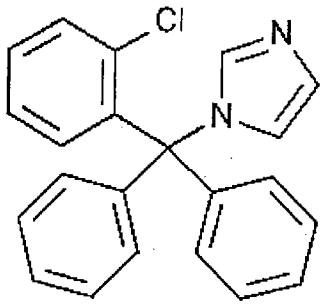
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-(o-chloro-α,α-diphenybenzyl)imidazole. MW 344.8427, $C_{22}H_{17}ClN_2$, CAS 23593-75-1



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	As of 5/27/02	Reviewed by G. Kang
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
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	III			4			

[1] Action codes for DMF Table:
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Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Overall pending		
Methods Validation	N/A for DS (Compendial) DP MV - Pending		
Labeling	Pending		
Bioequivalence	Pending		
EA	Exclusion requested		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-387

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not approvable at this point. The applicant is being notified with several minor deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: The drug substance is described in the USP. The drug substance is manufactured by ——————— DMF —— describes the synthesis of the drug substance. This DMF was reviewed previously by Gil Kang and found to be adequate as of 5/27/02. The drug product manufacturer used one lot of the drug substance to make one batch of the drug product. The drug substance was fully tested by the ANDA holder as per USP specifications using current USP methods and all the test results were within the specifications. The firm is being asked to include specifications for residual solvents, OVI's and some additional impurities.

Drug product: The DP is described in the current USP as clotrimazole Lozenges and not as clotrimazole troches. The drug product is indicated for the local treatment of oropharyngeal candidiasis. The strength of active ingredient in each troche is 10 mg. Other inactive ingredients present in the drug product are ——— povidone, ——————— (modified cellulose gum), ——————— and magnesium stearate. All the inactive ingredients are either USP of NF grade. A ——————— troche batch was manufactured by the firm and packaged in HDPE bottles of 70 count, 140 count and 500 count. In addition, the firm states that for the exhibit batch , a unit dose packaging of 10 troches per card is packaged. However, the packaging records show that — tablets/pouch are packaged for this lot. It is not clear what is the actual packaging configuration for the unit dose packaging. The firm has provided 3 month accelerated and 9 month room temperature stability data for the drug product in each container closure. The data meets all the stability specifications and justifies the proposed 24-month expiration date.

B. Description of How the Drug Product is Intended to be Used
Local treatment of oropharylgeal candidiasis.

C. Basis for Approvability or Not-Approval Recommendation

The deficiencies are minor and they are being communicated to the applicant. It is expected that the applicant will be able to address them in relatively short time.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-620/Ramesh Sood, Ph.D./6/28/02 7/30/02
HFD-620/Jim Fan/7/7/02 7/30/02

C. CC Block

ANDA 76-387
ANDA DUP 76-387
DIV FILE
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information from

CHEMISTRY REVIEW #1

3. All facilities referenced in your ANDA should be in compliance with CGMP at the time of approval.

4. Since the drug product is not a USP product, your drug product analytical methods will be validated by a FDA district laboratory after all the specification related issues are satisfactorily resolved.

Sincerely yours,

Paul Shrivastava 8/4/02

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

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-387
ANDA DUP 76-387
DIV FILE
Field Copy

Endorsements:

HFD-620/Ramesh Sood, Ph.D. / RKS 6/28/02 for NN 7/30/02

HFD-620/Jim Fan/ 7/7/02 7/30/02

HFD-617/S. Ho, PM/ 7/10/02 7/30/02

F/T by:
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TYPE OF LETTER: NOT APPROVABLE - MINOR

ANDA 76-387

Clotrimazole Troche, 10 mg

Roxane Laboratories, Inc.

Nashed E. Nashed, Ph.D.

Division 1

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. ANDA 76-387 (First Generic)

2. REVIEW #: 3 2

3. REVIEW DATE: 8/8/03

4. REVIEWER: Nashed E. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	Mar 28, 2002
New Correspondence	May 20, 2002
Minor Amendment	9/18/02
Amendment (Labeling)	12/30/02
Telephone Amendment	1/31/03
Telephone Amendment	4/8/03
Bio Amendment	7/17/03
Gratuitous Amendment	7/21/03
Bio Amendment	9/16/03

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc.

Address: 1809 Wilson Road, Columbus, OH 43228

Chemistry Review Data Sheet

Representative: Elizabeth Ernst

Telephone: 614-272-4785

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Clotrimazole Troche

9. LEGAL BASIS FOR SUBMISSION: The basis for this ANDA is Bayer Corporations's Mycelex (clotrimazole) Troche, 10 mg (NDA 18713). The firm also states that, in its opinion, there are no unexpired patents or marketing exclusivity indicated for the RLD.

10. PHARMACOL. CATEGORY: Local treatment of oropharygeal candidiasis.

11. DOSAGE FORM: Troche

12. STRENGTH/POTENCY: 10 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: x___Rx ___OTC

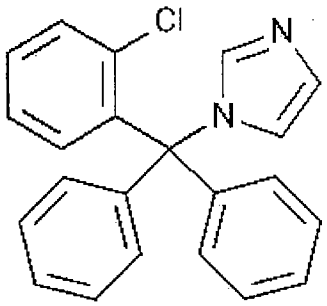
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-(o-chloro-α,α-diphenybenzyl)imidazole. MW 344.8427, $C_{22}H_{17}ClN_2$, CAS 23593-75-1



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A. DMFs:

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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	1/16/03	
Methods Validation	Ds and DP are Compendial		
Labeling	Acceptable	1/10/03	B. Weitzman
Bioequivalence	Deficient	12/17/03	C. Kim
EA	Exclusion requested		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __XX__ No If no, explain reason(s) below:

The application is MINOR

The Chemistry Review for ANDA 76-387

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not approvable – Bio is deficient.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: The drug substance is described in the USP. The drug substance is manufactured by ——————— DMF —— describes the synthesis of the drug substance. This DMF was reviewed previously by Gil Kang and found to be adequate as of 5/27/02. The drug product manufacturer used one lot of the drug substance to make one batch of the drug product. The drug substance was fully tested by the ANDA holder as per USP specifications using current USP methods and all the test results were within the specifications.
Drug product: The DP is described in the current USP as clotrimazole Lozenges and not as clotrimazole troches. The drug product is indicated for the local treatment of oropharyngeal candidiasis. The strength of active ingredient in each troche is 10 mg. Other inactive ingredients present in the drug product are povidone, ——— (modified cellulose gum), ——————— and magnesium stearate. All the inactive ingredients are either USP of NF grade. A ——— troche batch was manufactured by the firm and packaged in HDPE bottles of 70 count, 140 count and 500 count. In addition, the firm states that for the exhibit batch , a unit dose packaging of 10 troches per card is packaged. The firm has provided 3 month accelerated and 12 month room temperature stability data for the drug product in each container closure. The data meets all the stability specifications and justifies the proposed 24-month expiration date.

B. Description of How the Drug Product is Intended to be Used

Local treatment of oropharylgeal candidiasis.

C. Basis for Approvability or Not-Approval Recommendation

The application is not approvable – Bio is deficient (12/17/03).

III. Administrative

A. Reviewer's Signature N. Nashed 1/20/04

Nashed E. Nashed, Ph.D. 1/20/04

B. Endorsement Block

James M. Fan /8/8/03

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APPEARS THIS WAY
ON ORIGINAL

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CHEMISTRY REVIEW #2

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-387 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Clotrimazole Troche, 10 mg

The deficiency presented below represents a MAJOR deficiency.

A. Deficiency:

Bioequivalence deficiencies were communicated to you via facsimile on January 8, 2004. You should address the issues in the January 8, 2004 communication prior to or concurrent with your response to this communication.

Sincerely yours,

1/20/04

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

ANDA 76-387

Clotrimazole Lozenges USP, 10 mg
(Clotrimazole Troche, 10 mg)

Roxane Laboratories, Inc.

Nashed E. Nashed, Ph.D.

Division 1

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. ANDA 76-387 (First Generic)

2. REVIEW #: 3

3. REVIEW DATE: 6/24/04
   Revised: 7/13/04

4. REVIEWER Nashed E. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	Mar 28, 2002
New Correspondence	May 20, 2002
Minor Amendment	9/18/02
Amendment (Labeling)	12/30/02
Telephone Amendment	1/31/03
Telephone Amendment	4/8/03
Bio Amendment	7/17/03
Gratuitous Amendment	7/21/03
Bio Amendment	9/16/03
Major Amendment	2/17/04
Major Amendment	2/20/04
Amendment	2/26/04
Bio Amendment	3/10/04
Bio Amendment	4/2/04
Bio Amendment	5/4/04
Telephone Amendment	6/24/04
Controlled Correspondence	7/13/04
Telephone Amendment	7/26/04

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc.

Address: 1809 Wilson Road, Columbus, OH 43228

Representative: Elizabeth Ernst

Telephone: 614-272-4785

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Clotrimazole Lozenges

9. LEGAL BASIS FOR SUBMISSION:

The basis for this ANDA is Bayer Corporations's Mycelex® (clotrimazole) Troche, 10 mg (NDA 18-713). The firm has stated that, in its opinion, there are no unexpired patents or marketing exclusivity indicated for the RLD.

10. PHARMACOL. CATEGORY: Local treatment of oropharyngeal candidiasis.

11. DOSAGE FORM: Lozenge USP, 10 mg (Troche)

12. STRENGTH/POTENCY: 10 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: x___Rx ___OTC

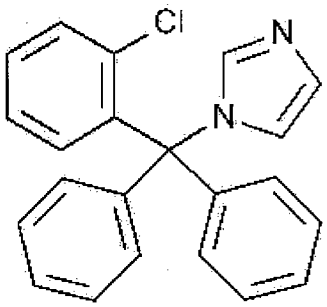
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-(o-chloro-α,α-diphenybenzyl)imidazole. MW 344.8427, $C_{22}H_{17}ClN_2$, CAS 23593-75-1



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	6/21/04	Reviewed by N.Nashed
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
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	III			4			

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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

APPEARS THIS WAY
ON ORIGINAL

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	1/16/03	
Methods Validation	Ds and DP are Compendial		
Labeling	Acceptable	1/10/03	B. Weitzman
Bioequivalence	Acceptable	5/14/04	S. Gunther
EA	Exclusion requested		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __XX__ No If no, explain reason(s) below:

The application is MINOR

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CHEMISTRY REVIEW #3

30. MICROBIOLOGY

Review status: N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

The DS is an USP item. Per John Grace, the DP is listed in the Orange Book a Clotrimazole Troche/Lozenge. Hence, the DP is also considered as a USP product. Therefore, FDA MV is not required for both the DS and DP.

32. LABELING

Labeling is acceptable 1/10/03.

33. ESTABLISHMENT INSPECTION

EER is acceptable 1/16/03

34. BIOEQUIVALENCE

Bio is acceptable on 5/14/04 by A. Gunther.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Review status: Satisfactory

Exclusion from requirement for environmental assessment statement is provided (volume 1.3, page 1273).

CC: ANDA 76-387
Division File
Field Copy

Endorsements:

HFD-627/N.Nashed/6/24/04 NN 7/13/04
HFD-627/627/J.Fan/6/24/04
HFD-617/A.Vu/6/24/04 7/13/04

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