CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-512

CHEMISTRY REVIEW(S)

NDA 21-512

LORATADINE TABLETS, 10 mg

L. PERRIGO COMPANY

Chong Ho Kim, Ph.D.
Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA #: 21-512

2. REVIEW #: 2

3. REVIEW DATE: 01-JUL-2003

4. REVIEWER: Chong Ho Kim, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	28-JUN-2002
Amendment [BL]	18-DEC-2002
Amendment[BC]	18-FEB-2003
Amendment[BZ]	04-MAR-2003
Amendment[BC]	12-MAR-2003
Amendment[BC]	18-MAR-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment[BC]	11-APR-2003
Amendment[AZ]	09-MAY-2003
Amendment[BC]	23-MAY-2003
Amendment[BC]	18-JUN-2003
Amendment[BC]	23-JUN-2003
Amendment[BC]	27-JUN-2003
Amendment[BC]	01-JUL-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Perrigo Company
Address:	515 Eastern Avenue, Allegan, MI 49010
Representative:	Ms. Valerie Gallagher
Telephone:	616-673-9367

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Not available(Original name was withdrawn)
   b) Nonproprietary Name (USAN): Loratadine Tablets, 10 mg
   c) Code Name/#:
   d) Chem. Type/Submission Priority:
      - Chem. Type: 3
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) Application

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg

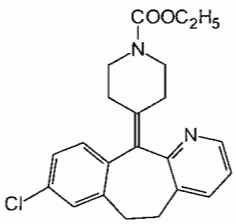
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx _X_ 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:



Loratadine

Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]-cyclohepta [1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate

Chemical Name: 11-[N-(ethoxycarbonyl)-4-piperidylidene]-8-chloro-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2-b]-pyridine
1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-ethyl ester

CAS Number: [79794-75-5]

Chemistry Review Data Sheet

Molecular Formula: $C_{22}H_{23}ClN_2O_2$

Molecular Weight: 382.89

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
	III			3	Adequate	9/19/02	See below (984C)
	III			3	Adequate	5/28/02	See below (1466C)
	III			3	Adequate	12/10/01	See below (3567C)
	III			3	Adequate	8/24/00	See below (3764C)
	III			3	Adequate	4/23/02	Dr. Frankewich's review dated 4/23/02
	III			3	Adequate	2/28/03	Dr. Heimann's review dated 2/28/03
	III			4	Adequate		Adequate information was provided in the NDA.
	II			3	Adequate	10/17/02	See below (12650C)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
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)
[3] Include reference to location in most recent CMC review

984C: Dr. Kang reviewed the DMF for [redacted] *and found it adequate.*
1466C: Dr. Boal's review dated may 28, 2002 is most recent one. She found the DMF adequate to support [redacted]

Chemistry Review Data Sheet

3567C: Dr. Theodorakis recently reviewed the DMF ——— review dated 12/10/01).

3764C: Dr. Frankewich reviewed the DMF (——— and found it adequate (review dated 8/24/00).

12650C: Dr. Dhanesar (HFD-623) reviewed annual update with regard to ——— and found it adequate. I concur with Dr. Dhanesar.

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
ANDA 76-301	Perrigo Co.				Under review

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
Claritin Tablets	N19-658/S-018	Schering Co.	The supplement was provided for the over-the-counter use of Claritin Tablets. Approved on 11/27/02
Claritin Syrup	N20-704/S-008	Schering Co.	The supplement was provided for the over-the-counter use of Claritin Syrup. Approved on 11/27/02
Claritin RadiTabs	N20-641/S-009	Schering Co.	The supplement was provided for the over-the-counter use of Claritin RediTabs. Approved on 11/27/02
Alavert OTC	N21-375	Wyeth Consumer Healthcare	Alavert (Loratadine) Orally Disintegrating Tablets was approved on 12/19/02

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			See stability data analysis on page 41 of review #1.
EES	——→ sites		Acceptable (4/2/03)	
Pharm/Tox	N/A			
Biopharm	**dissolution**			**See comments in the review**
LNC	N/A			
Methods Validation				Method validation has been initiated.
OPDRA	N/A			No trade name has been proposed.
EA	exclusion requested		acceptable /5-23-02	
Microbiology	N/A			

Chemistry Assessment Section

The Chemistry Review for NDA 21-512

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval is recommended from a CMC standpoint.

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

None

II. Summary of Chemistry Assessments

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

1). The loratadine drug substance is manufactured

Please note that the was withdrawn from this application

2). The formulation of loratadine 10 mg tablet is slightly different from the referenced drug. All excipients are compendial excipients.

3). Applicant has not proposed any proprietary name for this drug product.

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

This application is submitted for over-the-counter (OTC) loratadine tablets, 10 mg for the indication.

C. Basis for Approvability or Not-Approval Recommendation

1). Up to room temperature stability data and accelerated stability data on production-scale of drug product batches are provided. Applicant also provided hs stability data of bottle packages. With this sufficient actual stability data in hand, a biometrics consult on the proposed 24 months expiration dating period is not necessary.

2). EER is acceptable.

3). Method validation has been initiated.

4). All the deficiencies have been addressed. Chemist recommends approval of this NDA.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Chong Ho Kim/ 1-JUL-2003
ChemistryTeamLeaderName/Date: Guirag Poochikian/
ProjectManagerName/Date: Anthony Zeccola/

D. CC Block

Orig. NDA #21-512
HFD-570/Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/AZeccola
R/D Init. by:

Doc: n21-512r2.701

39 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chong-Ho Kim
7/2/03 01:40:25 PM
CHEMIST

Guiragos Poochikian
7/2/03 05:00:43 PM
CHEMIST

NDA 21-512

LORATADINE TABLETS, 10 mg

L. PERRIGO COMPANY

Chong Ho Kim, Ph.D.
Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA #: 21-512

2. REVIEW #: 1

3. REVIEW DATE: 14-APR-2003

4. REVIEWER: Chong Ho Kim, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-JUN-2002
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Representative:	Ms. Valerie Gallagher
Telephone:	616-673-9367

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b) Nonproprietary Name (USAN):	Loratadine Tablets, 10 mg
c) Code Name/#:	
d) Chem. Type/Submission Priority:	

Chemistry Review Data Sheet

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) Application

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg

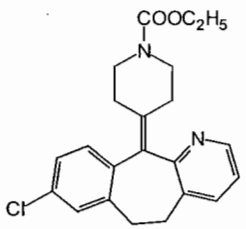
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___Rx __X__ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note20]:
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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



Loratadine

Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]-cyclohepta [1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate

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	III			3	Adequate	5/4/99	
	III			3	Adequate	12/10/01	See below*
	III			3	Adequate	8/24/00	See below**
	III			3	Adequate	5/7/99	
	III			3	Adequate	2/28/03	Dr. Heimann's review dated 2/28/03
	III			4	Adequate		Adequate information was provided in the NDA.
	II			3	Adequate	**10/17/02**	Dr. Dhanesar***
	II			3	Adequate	4/1//02	##

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[3] Include reference to location in most recent CMC review

** Dr. Theodorakis recently reviewed the DMF (review dated 12/10/01).*

** Dr. Frankewich reviewed the DMF (and found it adequate (review dated 8/24/00).

***Dr. Dhanesar (HFD-623) reviewed annual update with regard [redacted] and found it adequate. I concur with Dr. Dhanesar.

##Dr. Trimmer (HFD-623) reviewed the most recent amendment dated February 22, 2002 with regard to [redacted] and found it adequate. I concur with Dr. Trimmer.

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
ANDA 76-301	Perrigo Co.				Under review

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
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18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			See stability data analysis on page 41 of this review.
EES	[redacted] sites		Acceptable (4/2/03)	
Pharm/Tox	N/A			
Biopharm	**dissolution**			**See comments in the review**
LNC	N/A			
Methods Validation				*
OPDRA	acceptability of the trade name		pending	
EA	exclusion requested		acceptable /5-23-02	
Microbiology	N/A			

* Method validation will be deferred until pending method- related issues are fully resolved.

Chemistry Assessment Section

The Chemistry Review for NDA 21-512

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable from a CMC standpoint.

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

None

II. Summary of Chemistry Assessments

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

1). *This application is submitted for over-the-counter (OTC) loratadine tablets, 10 mg for the indication*

2). *Up to room temperature stability data and accelerated stability data on production-scale of drug product batches are provided. Applicant also provided stability data of bottle packages. With this sufficient actual stability data in hand, a biometrics consult on the proposed 24 months expiration dating period is not necessary.*

3). *Method validation will be deferred until pending issues are completely resolved.*

4). *The loratadine drug substance is manufactured by*

The DMF are adequate to support the current NDA.

5). *The formulation of loratadine 10 mg tablet is slightly different from the referenced drug. All excipients are compendial excipients.*

6). EER is acceptable.

7). *Previously proposed name withdrawn*

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

The drug product is loratadine 10 mg tablets. It will be used for the

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable. However, acceptable EER for all cited sites should be received from OC and the pending deficiencies listed at the end of the review should be addressed to gain approval.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Chong Ho Kim/ 02-APR-2003
ChemistryTeamLeaderName/Date: Guirag Poochikian/
ProjectManagerName/Date: Anthony Zeccola/

C. CC Block

Orig. NDA #21-512
HFD-570/Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/AZeccola
R/D Init. by:

Doc: n21-512r1.414

Chemistry Assessment

42 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chong-Ho Kim
4/14/03 01:27:05 PM
CHEMIST

Guiragos Poochikian
4/14/03 03:14:23 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21512/000
Org Code : 570
Priority : 6S

Sponsor: PERRIGO CO
502 EASTERN AVE
ALLEGAN, MI 49010

Stamp Date : 01-JUL-2002
PDUFA Date : 01-MAY-2003
Action Goal :
District Goal: 02-MAR-2003

Brand Name : [redacted] (LORATADINE) TABLET 10 MG
Estab. Name:
Generic Name: LORATADINE TABLET
Dosage Form: (TABLET)
Strength : 10 MG

FDA Contacts:			
A. ZECCOLA	Project Manager	(HFD-570)	301-827-1058
C. KIM	Review Chemist	(HFD-570)	301-827-1050
G. POOCHIKIAN	Team Leader	(HFD-570)	301-827-1050

Overall Recommendation: ACCEPTABLE on 02-APR-2003by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN : [redacted] FEI : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-JAN-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

DMF No: [redacted] AADA:

Responsibilities:

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-APR-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1811666 FEI : 1811666

PERRIGO CO

WATER ST/HOOKER RD/EASTERN AVE

ALLEGAN, MI 49010

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-JAN-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-JAN-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION
