CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-565

CHEMISTRY REVIEW(S)

NDA 21-565

RELESTAT®
(Epinastine HCl Ophthalmic Solution) 0.05%
equivalent to epinastine, 0.044% or 0.44 mg/mL

Allergan Inc.

Yong-de Lu, Ph.D.

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

HFD-550

Table of Contents

Chemistry Review Data Sheet

1. **NDA 21-565**

2. REVIEW #: 2

3. REVIEW DATE: 10-Oct-2003

4. REVIEWER: Yong-de Lu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	19-Dec-2002
Amendment	11-July-2003
Amendment	18-July-2003
Amendment	01-Aug-2003
Amendment	25-Aug-2003
Amendment	10-Oct -2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	19-Sep-2003
Amendment	23-Sep-2003
Amendment	10-Oct-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Allergan Inc.

Address: 2525 Dupont Drive
P.O.Box 19534
Irvine, CA 92623-9534

Representative: Elizabeth Bancroft, Sr. Director of Regulatory Affairs

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Fax: 714-246-4272

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ELESTAT™
b) Non-Proprietary Name (USAN): Epinastine HCl Ophthalmic Solution
c) Code Name/#: AGN 190342-LF/AGN 196156-H/Formula 9262X
d) Chem. Type/Submission Priority:
- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: non-sedating antihistamine, H_1-receptor antagonist

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.05%

13. ROUTE OF ADMINISTRATION: Topical, Ophthalmic, One drop in each eye twice a day

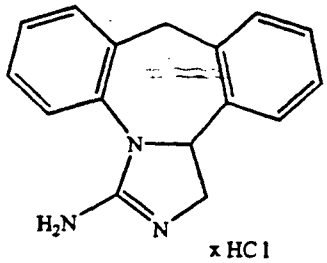
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. _____SPOTS product – Form Completed

__X__Not a SPOTS product

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

3-Amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine, hydrochloride



x HCl

Chemistry Review Data Sheet

$C_{16}H_{15}N_3 \bullet HCl$; MW: 285.— [108929-04-0]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	Boehringer Ingrelheim Parma. KG	API. epinastine	1	Adequate	07-July-03	Residual solvent tightened
[redacted]	III	[redacted]	[redacted]	3	Adequate	01-Mar-02	[redacted] Reviewed by V.Shah
[redacted]	III	[redacted]	[redacted]	3	Adequate	16-Oct-00	[redacted] Reviewed by Li Rodriguez
[redacted]	III	[redacted]	[redacted]	4	Adequate		Reported by Allergan
[redacted]	III	[redacted]	[redacted]	4	adequate		Reported by Allergan
[redacted]	III	[redacted]	[redacted]	3	Adequate	14-Feb-01	[redacted] Reviewed by Li Rodriguez

[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 NDA application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61,025	Epinastine HCl 0.05% Ophthalmic Solution
Patent	USP #4,313,931	Expiration Date: 02/23/01

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES (2 manufacturing sites, 1 testing site)	All Acceptable	20-May-03	J.Dambrogio (HFD-322)
Pharm/Tox	N/A		
LNC			
Methods Validation	Sent to District Labs	05-Sep-03	In progress
OPDRA	Trade name was modified		
EA	Claim of categorical exclusion is acceptable		
Microbiology	Approval	02-May-03	Vinayak Pawar

The Chemistry Review for NDA 21-565

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for **approval**.

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)

Epinastine is a racemic mixture of two stereo isomers. Results from the in-vitro receptor binding test indicate that both stereo isomers are equally potent.
The drug substance is manufactured and supplied by Boehringer Ingelheim Pharma KG, Germany (BI). The CMC information for the drug substance is reported in BI's DMF # [redacted] A letter of Authorization from BI is included.

The ophthalmic solution proposed in this application was originally developed by Boehringer Ingelheim Pharma KG, Germany (BI) and was subsequently licensed to Allergan in 1999.

Epinastine HCl ophthalmic solution is a clear, colorless, isotonic and sterile solution preserved with 0.01% benzalkonium chloride and [redacted] (w/v) edetate disodium. The solution pH is buffered and adjusted by the addition of monobasic sodium phosphate [redacted] and NaOH/HCl. All excipients used are USP/NF grade. The drug product will be manufactured, packaged and labeled at Allergan Waco, Texas facility. On-going stability testing is conducted at the Allergan Westport, Ireland facility.

Epinastine HCl 0.05% ophthalmic solution is manufactured by [redacted] The solution pH is adjusted to pH [redacted] by the addition of sodium hydroxide solution and/or hydrochloric acid prior to bringing to the final volume. The bulk solution is [redacted] filled into sterilized multi-dose low density polyethylene (LDPE) bottles. The scale-up process has been completed and validated at production batch sizes of [redacted] at the Allergan Waco facility.

The primary container closure for epinastine HCl 0.05% ophthalmic solution consists of a white bottle and a white tip manufactured from LDPE and a white cap manufactured from high impact polystyrene (HIPS). All bottles, tips, and caps are sterilized using , in a validated process. For commercial product, the caps will be sterilized.

Epinastine HCl 0.05% ophthalmic solution is expected to remain stable in the primary container/closure system under normal use conditions. The proposed expiration dating periods are 24 months for the commercial product

Post-approval stability protocol and stability commitment were acceptable.

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

Epinastine is a potent, topically active, direct H1-receptor antagonist. RELESTAT™ ophthalmic solution is indicated for the prevention of the signs and symptoms of allergic conjunctivitis.

The proposed drug product is packaged in packaging configurations: , 5 mL in an 8-mL bottle, and 10 mL in a 15-mL bottle. The 5 mL and 10 mL fill sizes are the proposed commercial configurations

The recommended dosage is one drop in each eye twice a day. Treatment should be continued throughout the period of exposure, even when symptoms are absent.

The product should be stored at 15^0C(59^0F) to 25°C (77°F) and keep bottle tightly closed when not in use.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments has ultimately provided adequate information on the chemistry, manufacturing and controls for the production of Epinastine HCl 0.05% Ophthalmic Solution. The acceptance criteria for pH value, osmolality and impurities concentration have been tightened to reflect the actual data observed in the long term stability study of the drug product. Meanwhile, the acceptance criteria of residual solvents for the drug substance epinastine HCl have been revised. Items on drop size testing, stability study updating, and labeling revision were also involved.

All deficiencies on labeling were addressed adequately and revised copies of mock up labels were provided.

The microbiology consult review for microbial evaluation of epinastine HCl 0.05% ophthalmic solution preserved with benzalkonium chloride and edetate disodium recommended an approval (5/2/03) action. All three manufacturing and testing sites were accepted by the Office of Compliance on 5/20/03.

III. Administrative

A. Reviewer's Signature

Signed electronically in DFS

B. Endorsement Block

Signed electronically by Chemistry Team Leader in DFS

C. cc Block

Original NDA 21-565
HFD-550/Chem Team Leader/LNg
HFD-830/CWChan
HFD-550/Chem Reviewer/YLu
HFD-550/CSO/RRodriguez
HFD-550/MED/WChambers

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/s/

Yong-De Lu
10/15/03 01:33:54 PM
CHEMIST

Linda Ng
10/15/03 01:50:34 PM
CHEMIST

NDA 21-565

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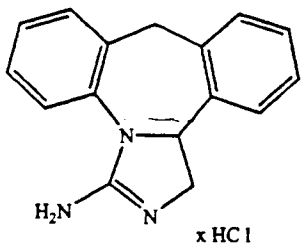

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Original NDA 21-565
HFD-550/Chem Team Leader/LNg
HFD-830/CWChan
HFD-550/Chem Reviewer/YLu
HFD-550/CSO/RRodriguez
HFD-550/MED/WChambers

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/s/

Yong-De Lu
9/11/03 03:16:08 PM
CHEMIST

Linda Ng
9/12/03 04:35:39 PM
CHEMIST