

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-127**

**CHEMISTRY REVIEW(S)**

**Division of Anti-inflammatory, Analgesic and  
Ophthalmologic Drug Products  
Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 21-127

**CHEMIST'S REVIEW #:** 1

**DATE OF REVIEW:** January 6, 2000

<b><u>SUBMISSION TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
Original NDA	08/03/1999	08/04/1999	08/06/1999
Amendment, BZ	08/19/1999	08/20/1999	08/30/1999
Amendment, BC	11/24/1999	11/26/1999	12/09/1999

**NAME & ADDRESS OF APPLICANT:**

ASTA Medica, Inc.  
890 East Street, Tewksbury, MA 01876.  
Contact: Ingeborg Army, MD, Telephone # 978-851-5981, Director, Regulatory Affairs.

**DRUG PRODUCT NAME**

Proprietary: Optivar™.

Established: Azelastine Hydrochloride Ophthalmic Solution, 0.05%.

Code Name/#: A5610 (ASTA Medica), W2979M (Carter Wallace), E-0659 (Eisai)

Chem.Type/Ther.Class: 3S.

**PHARMACOL. CATEGORY:** Selective H<sub>1</sub>-receptor antagonist. Proposed for the treatment of allergic conjunctivitis.

**DOSAGE FORM:** Ophthalmic Solution.

**STRENGTH:** 0.05% w/v.

**ROUTE OF ADMINISTRATION:** Topical ophthalmic drops.

**PROPOSED USUAL DOSAGE:** One drop instilled into each affected eye two times per day at an interval of 8 to 10 hours.

**DISPENSED:** By prescription only.       X  Rx      OTC

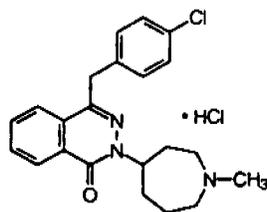
**CHEMICAL NAME(S), MOLECULAR FORMULA, MOLECULAR WEIGHT, CAS REGISTRY #, AND STRUCTURAL FORMULA:** See page 3-11.

**USAN, CAS:** (±)-1-(2H)-Phthalazinone, 4-((4-chlorophenyl)methyl)-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride.

**USAN alternate name:** (±)-4-(p-Chlorobenzyl)-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1-(2H)-phthalazinone monohydrochloride.

D,L-4-(4-Chlorobenzyl)-2-(perhydro-1-methylazepin-4-yl)-1-(2H)-phthalazinone,  
monohydrochloride.

C<sub>22</sub>H<sub>24</sub>ClN<sub>3</sub>O•HCl. MW = 418.37. CAS Registry # 79307-93-0.



Azelastine Hydrochloride – Structural Formula

**SUPPORTING DOCUMENTS:** See pages 2-4, 2-5 of the NDA.

**IND #** \_\_\_\_\_

Referenced NDA 20-114 (Letter of Authorization for referencing NDA 20-114 has been provided on page 151 of volume 1 of this NDA).

DMF#	Type	Holder	Item/Component	Review Date	Status
_____	II	ASTA Medica AG	_____	11/08/99	Inadequate
_____			_____		
_____			_____		
_____			_____		
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**CONSULTS:** The microbiology related CMC sections of the NDA were reviewed by the microbiology review staff of HFD-805, ONDC.



NDA 21-127  
Chemistry Review # 1

Page 4 of 55

cc:

Orig. NDA 21-127  
HFD-550/Division File  
HFD-550/Chemist/R.Uppoor  
HFD-550/Chem.TL/L.Ng  
HFD-830/C-w.Chen  
HFD-550/CSO/R.Rodriguez  
HFD-550/MO/W.Boyd  
HFD-550/DDD/W.Chambers.

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50 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

**Division of Anti-inflammatory, Analgesic and  
Ophthalmologic Drug Products  
Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 21-127

**CHEMIST'S REVIEW # 2**

**DATE OF REVIEW:** January 11, 2000

<b><u>SUBMISSION TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
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Original NDA	08/03/1999	08/04/1999	08/06/1999
Amendment, BZ	08/19/1999	08/20/1999	08/30/1999
Amendment, BC	11/24/1999	11/26/1999	12/09/1999

Contents of the above three submissions were reviewed in Chemist's Review # 1, dated 1/6/2000.

Amendment, BC	12/12/1999	12/14/1999	12/21/1999
Amendment, BC	12/17/1999	12/20/1999	12/21/1999

Contents of the above two submissions are reviewed in this review.

**NAME & ADDRESS OF APPLICANT:**

ASTA Medica, Inc.  
890 East Street, Tewksbury, MA 01876.  
Contact: Ingeborg Army, MD, Telephone # 978-851-5981, Director, Regulatory Affairs.

**DRUG PRODUCT NAME**

Proprietary: Optivar™.

Established: Azelastine Hydrochloride Ophthalmic Solution, 0.05%.

Code Name/#: A5610 (ASTA Medica), W2979M (Carter Wallace), E-0659 (Eisai)

Chem.Type/Ther.Class: 3S.

**PHARMACOL. CATEGORY:** Selective H<sub>1</sub>-receptor antagonist. Proposed for the treatment of allergic conjunctivitis.

**DOSAGE FORM:** Ophthalmic Solution.

**STRENGTH:** 0.05% w/v.

**ROUTE OF ADMINISTRATION:** Topical ophthalmic drops.

**PROPOSED USUAL DOSAGE:** One drop instilled into each affected eye two times per day at an interval of 8 to 10 hours.

**DISPENSED:** By prescription only.       Rx     OTC

**CHEMICAL NAME(s), MOLECULAR FORMULA, MOLECULAR WEIGHT, CAS  
REGISTRY #, AND STRUCTURAL FORMULA:** See page 3-11 of original NDA.



DMF#	Type	Holder	Item/Component	Review Date	Status

**CONSULTS:** The microbiology related CMC sections of the NDA were reviewed by the microbiology review staff of HFD-805, ONDC.

**CONCLUSIONS AND RECOMMENDATIONS:**

From the CMC review point of view this application is recommended for an APPROVABLE action. Deficiencies have been identified in the drug product analytical method. Deficiencies have also been found with respect to container-closures, stability protocol and post-approval stability commitment. Based on data provided in the application, a shelf-life of **eighteen months** is recommended for the drug product at this time. Revisions required in the chemistry, trademark and storage conditions sections of labeling have been identified. Validation of analytical methods at FDA laboratories will be requested after resolving all of the deficiencies identified in the analytical methods section of the application.

From the microbiology point of view, this application has been recommended for approval, pending the applicant's commitment to complete the studies indicated in the "List of Microbiology Comments" post-approval. The proposed trademark "Optivar" has been consulted out to CDER's OPDRA for their review and comment. An overall recommendation for the preapproval inspections requested for the drug substance and drug product manufacturing and testing sites is awaited from the CDER Office of Compliance. CMC related deficiencies and comments that should be communicated to the applicant are stated on page 16 of this review.

01/11/2000  
Rajendra Upoor, Ph.D., R.Ph.  
Review Chemist, HFD-830/550

1/12/00  
Linda Ng, Ph.D.  
Chemistry Team Leader, HFD-550

**REMARKS:** Drug product related CMC comments have been faxed to ASTA Medica on 12/20/1999 and 1/6/2000. Response(s) have not been received to those comments as of this date.

NDA 21-127  
Chemistry Review # 2

Page 4 of 16

cc:

Orig. NDA 21-127  
HFD-550/Division File  
HFD-550/Chemist/R.Uppoor  
HFD-550/Chem.TL/L.Ng  
HFD-830/C-w.Chen  
HFD-550/CSO/R.Rodriguez  
HFD-550/MO/W.Boyd  
HFD-550/DDD/W.Chambers.

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DIVISION OF ANTI\_INFLAMMATORY, ANALGESIC AND OPHTHALMOLOGIC DRUG  
PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-127

DATE REVIEWED: April 10, 2000

REVIEW #: 3

REVIEWER: Libaniel Rodriguez

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original NDA	08/03/1999	08/04/1999	08/06/1999
Amendment, BZ	08/19/1999	08/20/1999	08/30/1999
Amendment, BC	11/24/1999	11/26/1999	12/09/1999
Amendment, BC	12/12/1999	12/14/1999	12/21/1999
Amendment, BC	12/17/1999	12/20/1999	12/21/1999
The following amendments are the subject of this review.			
Amendment, BC	01/17/2000	01/27/2000	02/04/2000
Amendment, BC	02/07/2000	02/09/2000	02/11/2000
Amendment, NC	02/14/2000	02/16/2000	02/16/2000
Amendment, NZ	02/18/2000	02/22/2000	02/29/2000
Amendment, BC	03/09/2000	03/10/2000	03/16/2000
Amendment, BC	03/09/2000	03/10/2000	03/16/2000
Amendment, BC	03/10/2000	03/13/2000	03/16/2000
Amendment, BC	03/17/2000	03/20/2000	03/22/2000
Amendment, BC	03/24/2000	03/27/2000	04/03/2000

NAME & ADDRESS OF APPLICANT: Asta Medica Inc.  
890 East Street  
Tewksbury, MA 01876  
Contact: Ingeborg Army, MD  
Director of Regulatory Affairs  
Telephone # 978- 851-5981

DRUG PRODUCT NAME

Proprietary: Optivar

Established: Azelastine Hydrochloride Ophthalmic solution, 0.05 %.

Code Name/#: A5610 (ASTA Medica), W2979M (Carter Wallace), E-0659 (Eisai).

Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY/INDICATION: Selective H<sub>1</sub>-receptor antagonist. Proposed for treatment of allergic conjunctivitis.

DOSAGE FORM: Ophthalmic Solution

STRENGTHS: 0.05 % w/v

ROUTE OF ADMINISTRATION: Topical Ophthalmic Drops

PROPOSED USUAL DOSE: One drop instilled into each affected eye, two times per day at an interval of 8 to 10 hours.

Dispensed: By prescription only.

X Rx    OTC





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29 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

**DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMOLOGIC DRUG  
PRODUCTS**

**Review of Chemistry, Manufacturing, and Controls**

**NDA #: 21-127**

**DATE REVIEWED: May 12, 2000**

**REVIEW #: 4**

**REVIEWER: Libaniel Rodriguez**

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original NDA	08/03/1999	08/04/1999	08/06/1999
Amendment, BZ	08/19/1999	08/20/1999	08/30/1999
Amendment, BC	11/24/1999	11/26/1999	12/09/1999
Amendment, BC	12/12/1999	12/14/1999	12/21/1999
Amendment, BC	12/17/1999	12/20/1999	12/21/1999
Amendment, BC	01/17/2000	01/27/2000	02/04/2000
Amendment, BC	02/07/2000	02/09/2000	02/11/2000
Amendment, NC	02/14/2000	02/16/2000	02/16/2000
Amendment, NZ	02/18/2000	02/22/2000	02/29/2000
Amendment, BC	03/09/2000	03/10/2000	03/16/2000
Amendment, BC	03/09/2000	03/10/2000	03/16/2000
Amendment, BC	03/10/2000	03/13/2000	03/16/2000
Amendment, BC	03/17/2000	03/20/2000	03/22/2000
Amendment, BC	03/24/2000	03/27/2000	04/03/2000
The following amendments are the subject of this review.			
Amendment, BC	04/25/2000	04/26/2000	04/26/2000
Amendment, BC	04/26/2000	04/27/2000	
Amendment, BL	04/27/2000	05/01/2000	05/02/2000
Amendment, BL	04/28/2000	05/02/2000	05/08/2000
Amendment, BC	05/02/2000	05/03/2000	05/08/2000

**NAME & ADDRESS OF APPLICANT:** Asta Medica Inc.  
890 East Street  
Tewksbury, MA 01876  
Contact: Ingeborg Army, MD  
Director of Regulatory Affairs  
Telephone # 978- 851-5981

**DRUG PRODUCT NAME**

**Proprietary: Optivar**

**Established: Azelastine Hydrochloride Ophthalmic solution, 0.05 %.**

**Code Name/#: A5610 (ASTA Medica), W2979M (Carter Wallace), E-0659 (Eisai).**

**Chem.Type/Ther.Class: 3S**

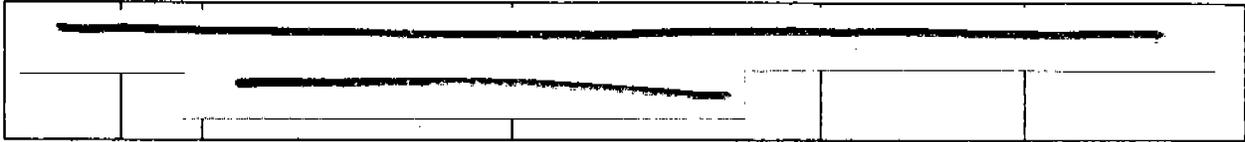
**PHARMACOL. CATEGORY/INDICATION: Selective H<sub>1</sub>-receptor antagonist. Proposed for treatment of allergic conjunctivitis.**

**DOSAGE FORM: Ophthalmic Solution**

**STRENGTHS: 0.05 % w/v**

**ROUTE OF ADMINISTRATION: Topical Ophthalmic Drops**





\* This type I DMF was not reviewed as per current CDER review practice.

**CONSULTS:** The microbiology related CMC sections of the NDA were reviewed by the microbiology review staff of HFD-805, ONDC.

NDA 21-127 was recommended for **approval** on March 7, 2000 by the review microbiologist. See microbiologist's review # 3 by Dr. Paul Stinavage.

**CONCLUSIONS & RECOMMENDATIONS:** The applicant responded adequately to all the questions and recommendations sent by the agency and provided the appropriate support data and commitments. Page 4 of this review contains a list of the phase 4 commitments made by the applicant. The applicant will be advised to change Osmolality for Osmolarity in the package insert. From the CMC perspective, NDA 21-127 is recommended for **APPROVAL**.

cc:

- Orig. NDA 21-127
- HFD-550/Division File
- HFD-550/Chemist/L. Rodriguez
- HFD-550/Chem. TL/L. Ng
- HFD-830/DD/C-W. Chen
- HFD-550/CSO/R. Rodriguez
- HFD-550/MO/W. Boyd
- HFD-550/DDD/W. Chambers



/S/

5-12-00

Libaniel Rodriguez, Ph.D.  
Review Chemist, HFD 550

/S/

5/12/00

Linda Ng, Ph. D.  
Chemistry Team Leader, HFD 550

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8 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Attachment 4

Application: NDA 21127/000  
Stamp: 04-AUG-1999 Regulatory Due: 04-JUN-2000  
Applicant: ASTA MEDICA (US)  
890 EAST ST  
TEWKSBURY, MA 018761496

Priority: 3S  
Action Goal:  
Brand Name: AZELASTINE HCL OPHTHALMIC SOLUTION 0.05%  
Established Name:  
Generic Name: AZELASTINE HCL OPHTHALMIC SOLUTION 0.05%  
Dosage Form: DRP (DROPS)  
Strength: 0.05%

Org Code: 550

District Goal: 05-APR-2000

FDA Contacts: R. RODRIGUEZ (HFD-550) 301-827-2090 , Project Manager  
L. RODRIGUEZ (HFD-830) 301-827-2069 , Review Chemist  
L. NG (HFD-830) 301-827-2511 , Team Leader

Overall Recommendation:

ACCEPTABLE on 17-APR-2000 by M. EGAS (HFD-322) 301-594-0095

Establishment: 9611095  
ASTA MEDICA AG  
D-4802  
HALLE-KUENSEBECK, , GM

DMF No: \_\_\_\_\_  
AADA No: \_\_\_\_\_

Profile: CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 23-MAR-2000  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION  
Profile: CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 23-MAR-2000  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Responsibilities: \_\_\_\_\_  
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Establishment: \_\_\_\_\_  
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DMF No:  
AADA No:

Profile: SNI OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 21-MAR-2000  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

Responsibilities: \_\_\_\_\_  
\_\_\_\_\_

Establishment: \_\_\_\_\_  
\_\_\_\_\_

DMF No: \_\_\_\_\_  
AADA No: \_\_\_\_\_

