CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-545

CHEMISTRY REVIEW(S)

NDA 21-545

Olopatadine HCl Ophthalmic Solution, 0.2% (expressed as free base)

Alcon Inc.

Linda Ng, Ph.D.
Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

HFD-550

Chemistry Review Data Sheet

1. NDA 21-545

2. REVIEW #: 3

3. REVIEW DATE: 21-Dec-2004

4. REVIEWER: Linda Ng, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Amendment	06-May-2004
Amendment	12-Mar-2004
Amendment	21-Apr-2003
Amendment	09-Apr-2003
Amendment	14-Mar-2003
Amendment	28-Feb-2003
Amendment	06-Feb-2003
Amendment	17-Jan-2003
Original	14-Aug-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	05-Nov-2004
Amendment	09-Dec-2004
Amendment	17-Dec-2004

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Alcon Inc.	Alcon Research Ltd. (US Agent)
Address:	P.O.Box 62 Bosch 69 CH-6331 Hunenberg Switzerland	6201 S. Freeway Fort Worth, TX 76134-2099
Representative:	Angela C. Kothe, OD, Ph.D, Assistant Director of Regulatory Affairs	
Telephone:	817-551-4933	
Facsimile:	817-551-4630	

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	None proposed
a) Non-Proprietary Name (USAN):	olopatadine HCl ophthalmic solution 0.2%
b) Code Name/#:	101788
c) Chem. Type/Submission Priority:	
• Chem. Type:	3
• Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Selective histamine H1-receptor antagonist and mast cell stabilizer. Indicated for

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.2%

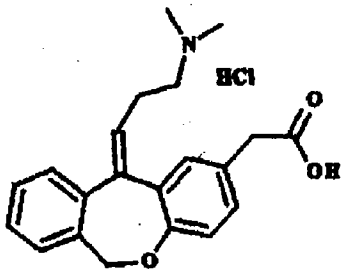
13. ROUTE OF ADMINISTRATION: Topical, Ocular, one drop per eye once-daily

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:



11-[(Z)-3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[*b,e*]oxepin-2-acetic acid, hydrochloride.$C_{21}H_{23}NO_3 \bullet HCl$, MW 373.88, [140462-76-6],Code Name: AL∅4943

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II	[redacted]	[redacted]	1	Adequate	25-Feb-03	deficiencies addressed
	III			3	Adequate	01-Mar-02	USP qualification data are in NDA
	III			3	Adequate	13-Dec-99	no revised information
	III			1	Adequate	24-Feb-03	deficiencies addressed
	III			1	Adequate	06-Mar-03	[redacted]
	III			1	Adequate	06-Mar-03	Alcon Code: [redacted]

Chemistry Review Data Sheet

	I	2			
	I	2			
	I	2			
	III	1	Adequate	30-Aug-00	
		6	Adequate	2/10/03	Information provided
	III	1	Adequate	2/10/03	

[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	44,216	Olopatadine ophthalmic solution 0.1%
NDA	20-688	Patanol (olopatadine ophthalmic solution) 0.1%

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES (3 manufacturing sites)	All 3 sites are acceptable	04-Nov-03	Shawnte Adams
Pharm/Tox			
LNC			
Methods Validation	None sent(Rev #1, p.76)		
OPDRA			
EA	Exclusion request		Yongde Lu
Microbiology	approval	19-Sep-02	Paul Stinavage

The Chemistry Review for NDA 21-545

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls perspective, the NDA is recommended for an approval action.

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)

In order to [redacted] while maintaining its safety and efficacy in the treatment of ocular itching [redacted] associated with allergic conjunctivitis, a once-daily dosing regimen of Olopatadine Hydrochloride Ophthalmic Solution (0.2% as base) has been developed.

The formulation chosen is based on that of PATANOL® with the following exceptions:
1) The concentration of olopatadine was increased from 0.1% to 0.2%.
2) Povidone at a concentration of [redacted]
3) Edetate disodium [redacted]

Olopatadine Ophthalmic Solution, 0.2% is a [redacted], sterile, preserved ophthalmic solution containing [redacted] w/v olopatadine hydrochloride (equivalent to 0.2 % olopatadine free base). Olopatadine hydrochloride is a structural analog of doxepine, a unique anti-allergy molecule in that it possesses both antihistamine and mast cell stabilizing activities with long duration of activity.

For the majority of chemistry, manufacturing and control information regarding olopatadine hydrochloride, the reference is made to the drug substance section of Alcon's NDA 20-688 for PATANOL® (Olopatadine Ophthalmic Solution, 0.1%). The supplier of olopatadine hydrochloride is [redacted] DMF [redacted] for olopatadine hydrochloride has been reviewed and found adequate to support this NDA. A copy of the Letter

of Authorization from [redacted] authorizing Agency to reference this DMF is located in V1, M1, Section 3.A.7, page 2.

The drug product is [redacted]

A Microbiology consult review recommended an approval action on 9/19/02.

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

Olopatadine Hydrochloride Ophthalmic Solution (0.2% as base) is an anti-allergy compound intended for once-daily topical ocular use. Olopatadine Hydrochloride Ophthalmic Solution (0.1% as base) was approved for marketing in US in December 1996 (NDA 20-688, PATANOL®) for the treatment of itching and subsequently in March 2000 (NDA 20-688/S-012) for the signs and symptoms of allergic conjunctivitis. The approved treatment regimen is twice daily. Now PATANOL® is marketed in over 30 countries including European and Canada.

Olopatadine Ophthalmic Solution, 0.2% is supplied in sterile white opaque LDPE DROP TAINER bottles and natural plugs, with a white polypropylene closures as follows: 2.5 mL filled in oval 4 mL bottle (NDC 0065-0272-25)

The recommended dose is one drop in each affected eye once daily.

The drug product is granted 24 months expiration dating period for trade size [redacted]

The product is permitted to be stored at 2 -25°C (36-77°F) (refrigeration and room temperature)

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided adequate information on the chemistry, manufacturing and controls for the production of Olopatadine Hydrochloride Ophthalmic Solution, 0.2% (free base) . The acceptance criteria in the drug substance and drug product specifications reflect the actual data observed in the long term stability study of the drug product.

The confusing packaging configuration of the drug product have been clarified and only one packaging configuration (2.5 mL fill in 4 mL bottle) for the trade size will be on the market.

[redacted]

III. Administrative

A. Reviewer's Signature

Signed electronically in DFS

B. Endorsement

Signed electronically by Acting Division Director in DFS

cc:

Original NDA 21-545
HFD-550/Chem Team Leader/LNg
HFD-830/DLin
HFD-550/Chem Reviewer/YLu
HFD-550/CSO/RRaphael
HFD-550/MED/WChambers

4 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 1 of 3

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

/s/

Linda Ng
12/21/04 04:39:12 PM
CHEMIST

David T. Lin
12/21/04 04:44:31 PM
CHEMIST
I concur.

NDA 21-545

[redacted]

(Olopatadine HCl Ophthalmic Solution) 0.2%(free base)

Alcon Inc.

Yong-de Lu, Ph.D.
Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

HFD-550

Chemistry Review Data Sheet

1. NDA 21-545

2. REVIEW #: 2

3. REVIEW DATE: 27-Apr-2004

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Amendment	21-Apr-2003
Amendment	09-Apr-2003
Amendment	14-Mar-2003
Amendment	28-Feb-2003
Amendment	06-Feb-2003
Amendment	17-Jan-2003
Original	14-Aug-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	06-May-2004
Amendment	12-Mar-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Alcon Inc.	Alcon Research Ltd. (US Agent)
Address:	P.O.Box 62 Bosch 69 CH-6331 Hunenberg Switzerland	6201 S. Freeway Fort Worth, TX 76134-2099
Representative:	Angela C. Kothe, OD, Ph.D, Assistant Director of Regulatory Affairs	
Telephone:	817-551-4933	
Facsimile:	817-551-4630	

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: [redacted]
b) Non-Proprietary Name (USAN): olopatadine HCl ophthalmic solution 0.2%
c) Code Name/#: 101788
d) Chem. Type/Submission Priority:
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Selective histamine H1-receptor antagonist and mast cell stabilizer. Indicated for [redacted]

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.2%

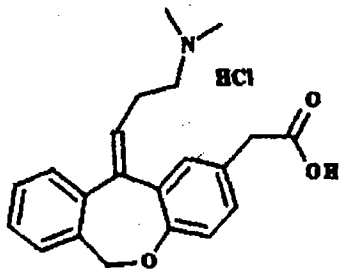
13. ROUTE OF ADMINISTRATION: Topical, Ocular, one drop per eye once-daily

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:



[1] Action codes for DMF Table:

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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	44,216	Olopatadine ophthalmic solution 0.1%
NDA	20-688	Patanol (olopatadine ophthalmic solution) 0.1%

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES (3 manufacturing sites)	All 3 sites are accepted		
Pharm/Tox			
LNC			
Methods Validation	None sent(Rev #1, p.76)		
OPDRA			
EA	Exclusion request		Yongde Lu
Microbiology	approval	19-Sep-02	Paul Stinavage

Chemistry Review Data Sheet

11-[(Z)-3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[*b,e*]oxepin-2-acetic acid, hydrochloride.$C_{21}H_{23}NO_3 \bullet HCl$, MW 373.88, [140462-76-6],Code Name: AL∅4943

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		D	1	Adequate	25-Feb-03	deficiencies addressed
	III			3	Adequate	01-Mar-02	USP qualification data are in NDA
	III			3	Adequate	13-Dec-99	no revised information
	III			1	Adequate	24-Feb-03	deficiencies addressed
	III			1	Adequate	06-Mar-03	
	III			1	Adequate	06-Mar-03	Alcon Code:
	I			2			
	I			2			
	I			2			
	III			1	Adequate	30-Aug-00	
				6	Adequate	2/10/03	Information provided
	III			1	Adequate	2/10/03	

The Chemistry Review for NDA 21-545

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls perspective, the NDA is recommended for an **approval** action.

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)

In order to [redacted] while maintaining its safety and efficacy in the treatment of ocular itching [redacted] associated with allergic conjunctivitis, a once-daily dosing regimen of Olopatadine Hydrochloride Ophthalmic Solution (0.2% as base) has been developed.

The formulation chosen is based on that of PATANOL® with the following exceptions:
1) The concentration of olopatadine was increased from 0.1% to 0.2%.
2) Povidone at a concentration [redacted]
3) Edetate disodium [redacted]

Olopatadine Ophthalmic Solution, 0.2% is a [redacted], sterile, preserved ophthalmic solution containing [redacted] w/v olopatadine hydrochloride (equivalent to 0.2 % olopatadine free base). Olopatadine hydrochloride is a structural analog of doxepine, a unique anti-allergy molecule in that it possesses both antihistamine and mast cell stabilizing activities with long duration of activity.

For the majority of chemistry, manufacturing and control information regarding olopatadine hydrochloride, the reference is made to the drug substance section of Alcon's NDA 20-688 for PATANOL® (Olopatadine Ophthalmic Solution, 0.1%). The supplier of olopatadine hydrochloride is [redacted] DMF [redacted] for olopatadine hydrochloride has been reviewed and found adequate to support this NDA. A copy of the Letter of Authorization from [redacted] authorizing Agency to reference this DMF is located in V1, M1, Section 3.A.7, page 2.

The drug product is —

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

Olopatadine Hydrochloride Ophthalmic Solution (0.2% as base) is an antiallergy compound intended for once-daily topical ocular use. Olopatadine Hydrochloride Ophthalmic Solution (0.1% as base) was approved for marketing in US in December 1996 (NDA 20-688, PATANOL®) for the treatment of itching and subsequently in March 2000 (NDA 20-688/S-012) for the signs and symptoms of allergic conjunctivitis. The approved treatment regimen is twice daily. Now PATANOL® is marketed in over 30 countries including European and Canada.

— (olopatadine Ophthalmic Solution, 0.2%) is supplied in sterile white opaque LDPE DROP TAINER bottles and natural plugs, with a white polypropylene closures as follows:

The recommended dose is one drop in each affected eye once daily.

The drug product is granted — expiration dating period for trade size —

The product is permitted to be stored at 2 -25°C (36-77°F) (refrigeration and room temperature)

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 Olopatadine Hydrochloride Ophthalmic Solution, 0.2% (free base) . The acceptance criteria for assay of impurities, osmolality and pH value have been tightened to reflect the actual data observed in the long term stability study of the drug product.

The confusing packaging configuration of the drug product have been clarified and only one packaging configuration (2.5 mL fill in — bottle) for the trade size drug product will be on the market.

Details can be found in the review for the Labeling Section.

The pending field inspection for Alcon Laboratory Inc.'s facility at Kaysersberg, France (CFN 9615703) was completed and recommended acceptable on 6/23/03 by Office of Compliance.

A Microbiology consult review recommended an approval action on 9/19/02.

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 21-545
HFD-550/Chem Team Leader/LNg
HFD-830/DLin
HFD-550/Chem Reviewer/YLu
HFD-550/CSO/RRaphael
HFD-550/MED/WChambers

9 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 2 of 3

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

/s/

Yong-De Lu
6/1/04 03:59:36 PM
CHEMIST

Linda Ng
6/2/04 09:03:28 AM
CHEMIST

NDA 21-545

TRADEMARK®
(Olopatadine HCl Ophthalmic Solution) 0.2%

Alcon 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 21-545

2. REVIEW #: 1

3. REVIEW DATE: 01-May-2003

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	21-Apr-2003
Amendment	09-Apr-2003
Amendment	14-Mar-2003
Amendment	28-Feb-2003
Amendment	06-Feb-2003
Amendment	17-Jan-2003
Original	14-Aug-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Alcon Inc.	Alcon Research Ltd. (US Agent)
Address:	P.O.Box 62 Bosch 69 CH-6331 Hunenberg Switzerland	6201 S. Freeway Fort Worth, TX 76134-2099
Representative:	Angela C. Kothe, OD, Ph.D, Assistant Director of Regulatory Affairs	
Telephone:	817-551-4933	
Facsimile:	817-551-4630	

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	TRADEMARK®
b) Non-Proprietary Name (USAN):	olopatadine HCl ophthalmic solution 0.2%
c) Code Name/#:	101788
d) Chem. Type/Submission Priority:	
• Chem. Type:	3
• Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Selective histamine H1-receptor antagonist and mast cell stabilizer. Indicated for

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.2%

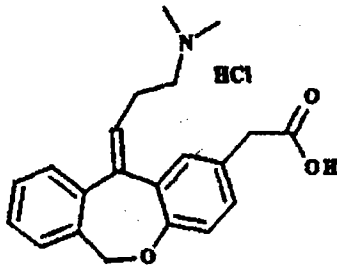
13. ROUTE OF ADMINISTRATION: Topical, Ocular, one drop per eye once-daily

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:



11-[(Z)-3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[*b,e*]oxepin-2-acetic acid, hydrochloride.$C_{21}H_{23}NO_3 \bullet HCl$, MW 373.88, [140462-76-6],Code Name: ALØ4943

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	25-Feb-03	deficiencies addressed
	III			3	Adequate	01-Mar-02	USP qualification data are in NDA
	III			3	Adequate	13-Dec-99	no revised information
	III			1	Adequate	24-Feb-03	deficiencies addressed
	III			1	Adequate	06-Mar-03	
	III			1	Adequate	06-Mar-03	Alcon Code:
	I			2			
	I			2			
	I			2			
	III			1	Adequate	30-Aug-00	
				6	Adequate	2/10/03	Information provided
	III			1	Adequate	2/10/03	

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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	44,216	Olopatadine ophthalmic solution 0.1%
NDA	20-688	Patanol (olopatadine ophthalmic solution) 0.1%

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES (3 manufacturing sites)	2 accepted, 1 scheduled		
Pharm/Tox			
LNC			
Methods Validation	none sent(Rev #1, p.76)		
OPDRA			
EA	Exclusion request		
Microbiology	approval	19-Sep-02	Paul Stinavage

The Chemistry Review for NDA 21-545

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls perspective, the NDA is recommended for **approvable** pending satisfactory results from the field inspection for Alcon Laboratories Inc.'s facility at Kaysersberg, France (CFN 9615703). In addition, packaging system configurations need further clarifications.

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)

In order to , while maintaining its safety and efficacy in the treatment of ocular itching associated with allergic conjunctivitis, a once-daily dosing regimen of Olopatadine Hydrochloride Ophthalmic Solution (0.2% as base) has been developed.

The formulation chosen is based on that of PATANOL® with the following exceptions:
1) The concentration of olopatadine was increased from 0.1% to 0.2%.
2) Povidone at a concentration
3) Edetate disodium

Olopatadine Ophthalmic Solution, 0.2% is a , sterile, preserved ophthalmic solution containing w/v olopatadine hydrochloride (equivalent to 0.2 % olopatadine free base). Olopatadine hydrochloride is a structural analog of doxepine, a unique anti-allergy molecule in that it possesses both antihistamine and mast cell stabilizing activities with long duration of activity.

For the majority of chemistry, manufacturing and control information regarding olopatadine hydrochloride, the reference is made to the drug substance section of Alcon's NDA 20-688 for PATANOL® (Olopatadine Ophthalmic Solution, 0.1%). The supplier of olopatadine hydrochloride is s DMF for olopatadine hydrochloride has been reviewed and found adequate to support this NDA. A copy of the Letter

of Authorization from [redacted] authorizing Agency to reference this DMF is located in V1, M1, Section 3.A.7, page 2.

The drug product is [redacted]

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

Olopatadine Hydrochloride Ophthalmic Solution (0.2% as base) is an antiallergy compound intended for once-daily topical ocular use. Olopatadine Hydrochloride Ophthalmic Solution (0.1% as base) was approved for marketing in US in December 1996 (NDA 20-688, PATANOL®) for the treatment of itching and subsequently in March 2000 (NDA 20-688/S-012) for the signs and symptoms of allergic conjunctivitis. The approved treatment regimen is twice daily. Now PATANOL® is marketed in over 30 countries including European and Canada.

PATANOL® E.S. (olopatadine Ophthalmic Solution, 0.2%) is supplied in sterile white opaque LDPE DROP TAINER bottles and natural plugs, with a white polypropylene closures as follows: [redacted] The recommended dose is one drop in each affected eye once daily.

The drug product is granted [redacted] expiration dating period for trade size [redacted]

The product is permitted to be stored at 2 -25°C (36-77°F) (refrigeration and room temperature)

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 Olopatadine Hydrochloride Ophthalmic Solution, 0.2% (free base) . The acceptance criteria for assay of impurities, osmolality and pH value have been tightened to reflect the actual data observed in the long term stability study of the drug product.

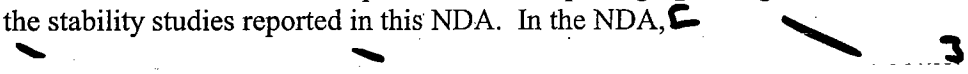
A Microbiology consult review recommended an approval action.. [redacted] facility for trade size dosage form and [redacted] site for the drug substance were approved by OC.

The **approvable** recommendation is based upon the pending satisfactory results from the field inspection for Alcon Laboratories Inc.'s facility at Kaysersberg, France (CFN 9615703) and the clarification on the packaging configurations.

A clarification for the NDC number for different bottle sizes was requested to the applicant. In response, however, in current amendment Alcon listed the following packaging configurations that intends to be marketed:

The following sample sizes for the drug product were submitted in the same amendment:

Alcon also claimed that these are the same product fills and packaging configurations which were used in the stability studies reported in this NDA. In the NDA,



Historically, Alcon has named bottles as per the typical fill in the bottle.

This statement is in contradiction with the paragraph cited from the NDA submission. Therefore, further clarifications need to be provided.

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 21-545
HFD-550/Chem Team Leader/LNg
HFD-830/CWChan
HFD-550/Chem Reviewer/YLu
HFD-550/CSO/RRaphael
HFD-550/MED/WChambers

76 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Yong-De Lu
5/1/03 02:44:52 PM
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Linda Ng
5/1/03 03:49:35 PM
CHEMIST