CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-228

CHEMISTRY REVIEW(S)

NDA 22-288

Bepotastine Besilate 1.5% Ophthalmic Solution

ISTA Pharmaceuticals, Inc.

Shrikant Pagay
ONDQA/OPS/DAIOP

Table of Contents

Chemistry Review Data Sheet

1. NDA #22-288

2. REVIEW #: 3 (Methods validation only)

3. REVIEW DATE: 2-September-2009

4. REVIEWER: Shrikant Pagay

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 66,864/ Original	12/20/06/
Amendment	9/10/08

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	11/12/08
Amendment	12/10/08
Amendment	7/2/09
Amendment	7/8/09
Amendment	7/31/09

7. NAME & ADDRESS OF APPLICANT:

Name: ISTA Pharmaceuticals Inc

Chemistry Review Data Sheet

Address:	15295 Alton Parkway, Irvine, CA 92618
Representative:	Paul Nowacki, Director, Regulatory Affairs
Telephone:	949-789-3109

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Bepreve
b) Non-Proprietary Name (USAN): Bepotastine Besilate
c) Code Name/# (ONDC only):TAU-284; SNJ-1773
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)

10. PHARMACOL. CATEGORY: Allergic Conjunctivitis

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 1.5% by weight

13. ROUTE OF ADMINISTRATION: Ophthalmic

14. Rx/OTC DISPENSED: x_Rx ___OTC

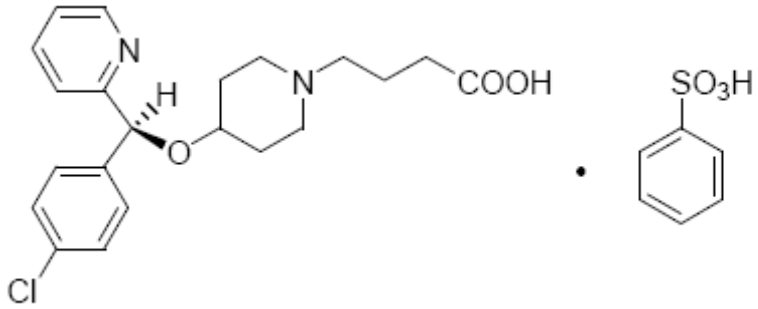
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___x___Not a SPOTS product

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

Proposed Name:

USAN Name: **(+) -4-[[(S) p-Chloro-alpha -2-pyridylbenzyl] oxy]-1-piperidine butyric acid monobenzenesulfonate**



$C_{21}H_{25}ClN_2O_3 \cdot C_6H_6O_3S$

MW: 547.06

Free acid Bepotastine MW. 388.90

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
19966	II	Ube Industries Ltd.	Bepotastine besilate	1	Adequate	4/4/09	
(b) (4)	III		(b) (4)	4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		
	III			4	NA		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
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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: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Methods Validation Consult	This application	9/1/09

18. STATUS: See below

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	1/26/09	S.Fergusion (Report attached)
Pharm/Tox	Safe (Volatile and semi-volatile leachable)	6/29/09	Theresa Allio
Biopharm	NA		
LNC	NA		
Methods Validation	Acceptable	9/1/09	B.J.Westenberger/Pagay
OPDRA (DMEPA)	Acceptable (Name)	2/5/09	Raichell Brown
EA	Acceptable	7/8/09	S.Pagay for Catagorical Exemption
Microbiology	(not a consult from CMC)	6/17/09	Metcalfe

OGD: NA

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for NDA 22-288

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval. Methods Validation studies from the FDA laboratory are completed and the methods are acceptable.

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

II. Summary of Chemistry Assessments

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

Drug Substance

Bepotastine besilate is manufactured by Ube Industries and the information for the NDA is submitted through DMF #19966. Bepotastine besilate is a white crystalline powder with no odor and bitter taste. It is very soluble in (b) (4) but sparingly soluble in (b) (4). It is stable when exposed to light, and optically active. The S-isomer is the active drug and (b) (4) is controlled as an impurity through synthesis. The distribution coefficient in 1-octanol is higher than in aqueous buffer in the pH 5-9 range. There are 10 potential impurities but only one impurity is above 0.1%. Two potential genotoxic impurities (b) (4) are controlled below (b) (4). Residual (b) (4) is controlled below (b) (4) Bepotastine besilate is stable under long term storage conditions for (25ºC/60% RH) over 5 years.

Drug Product

Bepotastine besilate was originally developed as an oral tablet dosage form and got approval in Japan in 2000 for allergic rhinitis. It is a non-sedating anti-allergic drug. The proposed NDA is an ophthalmic solution indicated for allergic conjunctivitis. Bepotastine besilate ophthalmic solution 1.5% is a sterile solution. It is an aqueous solution to be administered as drops at or near physiological pH range of tears. The formulation contains sodium chloride, monobasic sodium phosphate as dihydrate, benzalkonium chloride, sodium hydroxide and purified water; typically these components are used for (b) (4), preservative action, pH adjustment,

buffering capacity and a vehicle for administration, respectively. It was demonstrated during the formulation development that sodium chloride (b) (4) All excipients are of USP/NF grade. It is manufactured as a (b) (4) solution. (b) (4) The fill volumes are 1, 2.5, 5, and 10 mL. The release and stability testing includes all the typical tests for sterile ophthalmic solutions (description, assay, impurities, pH, osmolality, particulate matter, preservative assay, microbiological testing). Also, a one time testing included the following studies: freeze-thaw, weight gain/loss due to water vapor transmission from the container, semi-volatile and volatile leachable material released into the ophthalmic solution from the container and label. Stability data on 23 batches manufactured for clinical, non-clinical and registration studies (Primary and support batch data) supports 12 months shelf life for the 1 mL fill and 18 months for the 2.5, 5 and 10 mL fill sizes.

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

The drug product is a sterile solution and should be dispensed in its original container. The label should indicate that the solution is for topical use only and not for injection or oral use. Also, the label should indicate to not touch dropper tip to any surface as it may contaminate the contents. The usual dose is to instill one drop in the affected eye twice a day. The product is stored under ambient conditions (15ºC to 30ºC) and discarded as indicated on the manufacturer's label at expiration date.

C. Basis for Approvability or Not-Approval Recommendation

The following items are satisfactorily completed for approvability consideration:
DMF for the drug substance is adequate.
All manufacturing, testing and packaging facilities for the drug substance and the drug product received acceptable status from compliance ((EER attached to Review 1)
The drug substance and drug product quality is reproducible based on the batch analysis data for release and stability.
Manufacturing processes for the drug substance and the drug product are well controlled.
ISTA has provided satisfactory response to all deficiencies.
FDA laboratory conducted (b) (4) and the proposed methods for assay and impurities are acceptable.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

4 Page(s) have been Withheld in Full following this page as B4 (TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22288	ORIG-1	ISTA PHARMACEUTICALS	BEPOTASTINE BESILATE OPHTHALMIC SOLUTION

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/s/

SHRIKANT N PAGAY
09/15/2009

NORMAN R SCHMUFF
09/22/2009

MEMORANDUM

Date: August 13, 2009
To: NDA 22-288

From: Elaine Morefield, Ph.D.
Division Director
Pre-marketing Assessment Division II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-288, Bepreve (bepoststine besilate ophthalmic Solution) 1.5%.

I have assessed the ONDQA reviews of NDA 22-288, Bepreve (bepoststine besilate ophthalmic Solution) 1.5%. The sponsor has submitted data assuring that they can produce a quality product. Therefore, I concur with the ONDQA recommendation of approval from the CMC perspective.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22288	ORIG 1		BEPOTASTINE BESILATE OPHTHALMIC SOLUTION

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

/s/

ELAINE M MOREFIELD
08/13/2009

NDA 22-288

Bepotastine Besilate 1.5% Ophthalmic Solution

ISTA Pharmaceuticals, Inc.

Shrikant Pagay
ONDQA/OPS/DAIOP

Table of Contents

Chemistry Review Data Sheet

1. NDA #22-288

2. REVIEW #: 2

3. REVIEW DATE: 6-May-2009

4. REVIEWER: Shrikant Pagay

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 66,864/ Original	12/20/06/
Amendment	9/10/08

6. SUBMISSION(S) BEING REVIEWED:

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Address:	15295 Alton Parkway, Irvine, CA 92618
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8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Bepreve
b) Non-Proprietary Name (USAN): Bepotastine Besilate
c) Code Name/# (ONDC only):TAU-284; SNJ-1773
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)

10. PHARMACOL. CATEGORY: Allergic Conjunctivitis

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 1.5% by weight

13. ROUTE OF ADMINISTRATION: Ophthalmic

14. Rx/OTC DISPENSED: x_Rx ___OTC

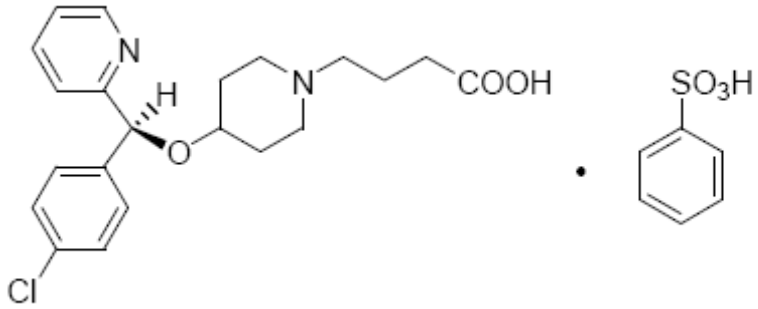
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___x___Not a SPOTS product

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

Proposed Name:

USAN Name: **(+) -4-[[(S) p-Chloro-alpha -2-pyridylbenzyl] oxy]-1-piperidine butyric acid monobenzenesulfonate**



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(b) (4)	III		(b) (4)	4	NA		
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	III			4	NA		
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	III			4	NA		

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[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: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS: See below

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	1/26/09	S.Fergusion (Report attached)
Pharm/Tox	Safe (Volatile and semi-volatile leachable)	6/29/09	Theresa Allio
Biopharm	NA		
LNC	NA		
Methods Validation	Pending response		Requested 7/28/09
OPDRA (DMEPA)	Accptable (Name)	2/5/09	Raichell Brown
EA	Acceptable	7/8/09	S.Pagay for Catagorical Exemption
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OGD: NA

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for NDA 22-288

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval. Methods Validation results from the FDA laboratory are pending, but this is not an approvability issue.

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

II. Summary of Chemistry Assessments

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

Drug Substance

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Manufacturing processes for the drug substance and the drug product are well controlled.
ISTA has provided satisfactory response to all deficiencies. However, results from FDA laboratory for [redacted] are pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

13 Page(s) have been Withheld in Full following this page as B4 (TS)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22288	ORIG 1		BEPOTASTINE BESILATE OPHTHALMIC SOLUTION
NDA 22288	ORIG 1		BEPOTASTINE BESILATE OPHTHALMIC SOLUTION
NDA 22288	ORIG 1		BEPOTASTINE BESILATE OPHTHALMIC SOLUTION

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/s/

SHRIKANT N PAGAY
08/06/2009

NORMAN R SCHMUFF
08/09/2009

NDA 22-288

Bepotastine Besilate 1.5% Ophthalmic Solution

ISTA Pharmaceuticals, Inc.

Shrikant Pagay
ONDQA/OPS/DAIOP

Table of Contents

Chemistry Review Data Sheet

1. NDA #22-288

2. REVIEW #:1

3. REVIEW DATE: 6-May-2009

4. REVIEWER: Shrikant Pagay

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 66,864/ Original Amendment	12/20/06/ 9/10/08

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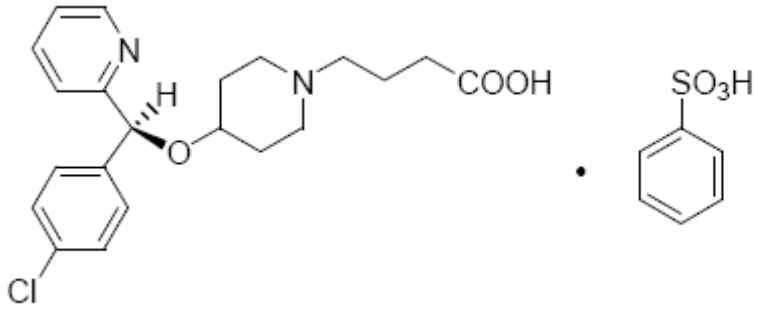
Proposed Name:

USAN Name: **(+) -4-[[(S) p-Chloro-alpha -2-pyridylbenzyl] oxy]-1-piperidine butyric acid monobenzenesulfonate**



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B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS: See below

ONDC:

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OGD: NA

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EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for A/NDA ##-###

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is not approved pending response for comments submitted to the sponsor.

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

II. Summary of Chemistry Assessments

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

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C. Basis for Approvability or Not-Approval Recommendation

The following items are satisfactorily completed:
DMF for the drug substance is adequate.
All manufacturing, testing and packaging facilities for the drug substance and the drug product received acceptable status for compliance ((Attached EER)
The drug substance and drug product quality is reproducible based on batch analysis data for release and stability.
Manufacturing processes are well controlled.

The only pending issue is Response to FDA comments

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

67 Page(s) have been Withheld in Full following this page as B4 (TS)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22288	ORIG 1	ISTA PHARMACEUTICALS	BEPOTASTINE BESILATE OPHTHALMIC SOLUTION

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/s/

SHRIKANT N PAGAY
07/27/2009

NORMAN R SCHMUFF
07/27/2009

Initial Quality Assessment
Branch __IV__
Pre-Marketing Assessment Division __II__

OND Division:	Division of Anti-Infective and Ophthalmology Produ
NDA:	22-288
Applicant:	ISTA Pharmaceuticals Inc
Stamp Date:	November 12, 2008
PDUFA Date:	September 12, 2009
Trademark:	Bepreve
Established Name:	Bepotastine Ophthalmic solution
Dosage Form:	Ophthalmic Solution 1.5%
Route of Administration:	topical
Indication:	Ocular itching associated with allergic conjunctivitis
PAL:	Linda Ng, Ph.D.

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☐	☒

Summary and Critical Issues: Note that NDA and DMF information are discussed in this IQA.

Summary

This NDA dated November 12, 2008 from ISTA Pharmaceutical Inc is an eCTD and was accepted as a 1S submission. Amendments dated December 10, 2008 contains proposed proprietary name, December 11 contains the container leachable study and December 18, 2008 contains the mock-up immediate container label and carton labeling.

Bepotastine besilate, a new molecular entity, is manufactured by Ube Industries Ltd, Japan and all information related to the drug substance is submitted to type II DMF 19,966. It is a salt and express as 1.5% free acid for the drug product in the label. Minimally information on the drug substance is in the NDA.

According to the DMF holder, bepotantine besilate is a white crystalline powder sparingly soluble in (b) (4) . Reference standard for the drug substance and impurities are mentioned. The starting material was an on-going discussion topic.

Bepotantine besilate reference standard (b) (4)

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/s/

Linda Ng
1/26/2009 12:42:42 PM
CHEMIST

Norman Schmuff
1/29/2009 06:03:40 PM
CHEMIST

NDA FILEABILITY CHECKLIST

NDA Number: 22-288
Applicant: ISTA Pharmaceuticals,
Letter Date: November 14, 2008
Stamp Date: November 14, 2008
Drug Name: Bepreve (bepotastine Besilate Ophthalmic Solution) 1.5% as acid

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) __Yes__

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	Y		
2	Is the section indexed and paginated adequately?	Y		eCTD submission
3	On its face, is the section legible?	Y		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	Y		
5	Is a statement provided that all facilities are ready for GMP inspection?	Y		In cover letter
6	Has an environmental assessment report or categorical exclusion been provided?	Y		M 1.12.14
7	Does the section contain controls for the drug substance?	Y		Bepotastine besilate manufactured in Ube Indutries Ltd, Japan. Type II DMF 19966
8	Does the section contain controls for the drug product?	Y		
9	Has stability data and analysis been provided to support the requested expiration date?	Y		One strength with 4 fill sizes of 1, 2.5, 5 and 10 mL. 3 batches 6 months stability RT and accelerated for all fill sizes provided. Has supporting stability data.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			On-going discussion on starting material. Applicant did not wait for Agency's response before submitting NDA
11	Have draft container labels been provided?	Y		In M1 – SPL provided
12	Has the draft package insert been provided?	Y		
13	Has an investigational formulations section been provided?	Y		Discussed in section 2.3.P.2 Pharmaceutical Development.
14	Is there a Methods Validation package?	Y		
15	Is a separate microbiological section included?			Information included. Section not obvious.

NDA 22-288

Chemistry Reviewer: Suresh Pagay, Ph.D.
Pharmaceutical Assessment Lead: Linda Ng, Ph.D.
Branch Chief: Norman Schmuff, Ph.D.
Prepared by: LNg 12/3/08

DMF Number	Holder	Description	LOA Included	Status
19966	Ube Industries Ltd	Bepotastine besilate	April 24, 2008	
		(b) (4)	July 3, 2007	
			June 4, 2007	
			June 28, 2007	
			June 4, 2007	
			June 8, 2007	
			June 6, 2007	
			May 19, 2006	
			May 30, 2008	

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/s/

Linda Ng
12/3/2008 02:29:22 PM
CHEMIST

Norman Schmuff
12/3/2008 02:47:44 PM
CHEMIST