

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022184Orig1s000**

**CHEMISTRY REVIEW(S)**

### Chemistry Review # 3

## NDA 22-184

### Bimatoprost Ophthalmic Solution, 0.01%

Allergan, Inc.

From the chemistry, manufacturing and controls standpoint, the recommendation for this NDA remains Approval.

This recommendation is supported by an overall acceptable recommendation (dated April 16, 2010) regarding the CGMP status of the facilities involved in the manufacture of the proposed drug substance and drug product made by the Office of Compliance. A copy of an acceptable EER is attached below (Attachment I).

Three amendments containing quality information have been submitted to this NDA since the last CMC review recommending approval (refer to Addendum to CMC Review # 2 dated May 1, 2008; also, note previous CMC reviews of this NDA in DARRTS, i.e., Review # 1 dated March 14, 2008 and Review # 2 dated April 18, 2008). Information provided in these amendments was reviewed and found acceptable.

#### **Amendment dated March 26, 2009**

This amendment contains a notification of a name change for drug substance supplier, from [REDACTED] (b) (4). The applicant stated that this is a change in name only. There have been no changes to the manufacturing and testing of bimatoprost. This submission contains the notification letter from [REDACTED] (b) (4) regarding the name change (Att 3.2.S.2.1-1) and updated sections 2.3.S.2 and 3.2.S.2.1 reflecting that change.

#### **Amendment dated April 28, 2009**

This amendment provides for an addition of specification for bacterial endotoxins for the drug product, which was submitted in response to the Agency request dated February 12, 2008. This submission includes a test method and a proposed limit of NMT [REDACTED] (b) (4) in the drug product specification. In addition, the applicant has added routine endotoxins testing for the bulk drug substance and excipients. The purified water [REDACTED] (b) (4) for the drug product must meet the same endotoxins requirements as Water for Injection (NMT [REDACTED] (b) (4)).

This submission was reviewed by quality microbiology reviewer, Dr. Bryan Riley and found acceptable (refer to the quality microbiology review dated June 8, 2009 in DARRTS). The specification table has been updated to include this addition (see

Attachment II, below). In addition, the stability section 3.2.P.8.2 was updated to include endotoxins testing on stability (see Attachment III, below).

**Amendment dated September 16, 2009**

This submission provides updated information regarding the manufacturing facilities, (this update was requested by the Agency and it was initially submitted via e-mail dated July 2, 2009). Two additional facilities for endotoxins testing were added with this amendment. The updated list of facilities includes the following sites:

Drug Substance:

**Table 2.3.S.2.1-1 Manufacturer for Bimatoprost Drug Substance**

(b) (4)



**Table 2.3.S.2.1-2 Locations Analyzing Bimatoprost Drug Substance**

Site	Address	Drug Establishment Registration Number	Responsibilities	Contact Name and Information
Allergan Sales, LLC.	8301 Mars Drive Waco, TX 76712 USA	1643525	Drug substance testing and release	Jose Toro Senior Director Quality Assurance Phone: 254-666-8795 Fax: 254-666-3012 E-Mail: toro_jose@allergan.com
Allergan Pharmaceuticals Ireland	Castlebar Road Westport, County Mayo, Ireland	3002806348	Drug substance testing and release	Siobhan Camplisson Director, QA & Development Phone: +353(98)5254 Fax: +3539825791 E-Mail: camplisson_siobhan@allergan.com

Drug Product:

**Table 2.3.P.3-1 Manufacturers for 0.01% Bimatoprost/200 ppm BAK Ophthalmic Solution**

Site	Address	Drug Establishment Registration Number	Responsibilities	Contact Name and Information
Allergan Sales, LLC.	8301 Mars Drive Waco, TX 76712 USA	1643525	Bulk manufacturing and aseptic filling. Packaging and labeling. Quality control testing of raw materials, intermediate, container-closure systems, and finished drug product. Manufacturing of container-closure systems.	Jose Toro Senior Director Quality Assurance Phone: 254-666-8795 Fax: 254-666-3012 E-Mail: toro_jose@allergan.com
(b) (4)				

**Table 2.3.P.3-1 Manufacturers for 0.01% Bimatoprost/200 ppm BAK Ophthalmic Solution (continued)**

Site	Address	Drug Establishment Registration Number	Responsibilities	Contact Name and Information
Allergan Pharmaceuticals Ireland	Castlebar Road Westport, Co Mayo Ireland	3002806348	Stability testing of finished drug product.	Denis Gallagher ETC Manager Phone: +353(98)55544 Fax: +3539825791 E-Mail: gallagher_denis@allergan.com
(b) (4)				

As stated above, the EER was submitted for this NDA and found acceptable on April 16, 2010.

# Attachment I

## FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

<b>Application:</b>	NDA 22184/000	<b>Sponsor:</b>	ALLERGAN
<b>Org. Code:</b>	520		1100 EAST BELL RD
<b>Priority:</b>	5S		PHOENIX, AZ 850699600
<b>Stamp Date:</b>	03-JUL-2007	<b>Brand Name:</b>	BIMATOPROST 0.01%
<b>PDUFA Date:</b>	03-MAY-2008	<b>Estab. Name:</b>	
<b>Action Goal:</b>		<b>Generic Name:</b>	BIMATOPROST 0.01%
<b>District Goal:</b>	04-MAR-2008	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	001; SOLUTION, DROPS; BIMATOPROST; .01%
<b>FDA Contacts:</b>	J. DAVID	Project Manager	301-796-4247
	D. MATECKA	Review Chemist	301-796-1415
	L. NG	Team Leader	301-796-1426

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<b>Overall Recommendation:</b>	ACCEPTABLE	on 16-APR-2010	by A. INYARD	()	
	ACCEPTABLE	on 30-APR-2008	by S. ADAMS	()	301-827-2443

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<b>Establishment:</b>	CFN: 1643525	FEI: 1643525		
	ALLERGAN INC 8301 MARS DR WACO, TX 767128578			
<b>DMF No:</b>	1528	<b>AADA:</b>	N 021275	
	2461		N 021668	
	3375			
<b>Responsibilities:</b>	DRUG SUBSTANCE RELEASE TESTER FINISHED DOSAGE LABELER FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE OTHER TESTER FINISHED DOSAGE PACKAGER FINISHED DOSAGE RELEASE TESTER			
<b>Profile:</b>	CONTROL TESTING LABORATORIES "ALSO" (DRUGS)	<b>OAI Status:</b>	NONE	
<b>Last Milestone:</b>	OC RECOMMENDATION			
<b>Milestone Date:</b>	23-OCT-2009			
<b>Decision:</b>	ACCEPTABLE			
<b>Reason:</b>	BASED ON PROFILE			
<b>Profile:</b>	OPHTHALMIC/STERILE NON-INJECTABLE	<b>OAI Status:</b>	NONE	
<b>Last Milestone:</b>	OC RECOMMENDATION			
<b>Milestone Date:</b>	03-NOV-2009			
<b>Decision:</b>	ACCEPTABLE			
<b>Reason:</b>	DISTRICT RECOMMENDATION			

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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

**Establishment:** CFN: 9616651 FEI: 3002806285  
ALLERGAN PHARMACEUTICALS IRELAND  
CASTLEBAR ROAD  
WESTPORT, CO. MAYO, IRELAND

**DMF No:** AADA:

**Responsibilities:** DRUG SUBSTANCE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 04-NOV-2009

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE OTHER TESTER

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 08-MAR-2010

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**Establishment:** CFN: (b) (4) FEI: (b) (4)  
(b) (4)

**DMF No:** AADA:

**Responsibilities:** FINISHED DOSAGE OTHER TESTER

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 26-OCT-2009

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22184	ORIG-1	ALLERGAN INC	BIMATOPROST 0.01%

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/s/

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DOROTA M MATECKA  
04/20/2010

STEPHEN P MILLER  
04/21/2010

**Addendum to CMC Review # 2 of NDA 22-184**

LUMIGAN 0.01%  
(bimatoprost ophthalmic solution)

Allergan, Inc.

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

An overall acceptable recommendation regarding the CGMP status of the facilities involved in the manufacture of the proposed drug substance and drug product was made by the Office of Compliance on April 30, 2008. A copy of an acceptable EER is included below (Attachment).

It should also be noted that this drug product is a Type 5 product (and not a Type 3 as it is stated under Chemical Type in the chemistry review # 1 of this NDA; item 8 of the Data Sheet).



Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : 9616651 FEI : 3002806285  
ALLERGAN PHARMACEUTICALS IRELAND  
CASTLEBAR ROAD  
, , EI

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 30-APR-08  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

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01-MAY-2008

FDA CDER EES

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ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Establishment : CFN : (b) (4) FEI : (b) (4)  
(b) (4)

DMF No: AADA: 021275

Responsibilities: (b) (4)

Profile : CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 25-SEP-07  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

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/s/

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Dorota Matecka  
5/1/2008 04:42:14 PM  
CHEMIST

Norman Schmuiff  
5/1/2008 07:46:58 PM  
CHEMIST

## **Chemistry Review # 2**

**NDA 22-184**

**Bimatoprost Ophthalmic Solution, 0.01%**

Allergan, Inc.

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval pending the overall recommendation to be made by the Office of Compliance regarding the CGMP status of the facilities involved in the manufacture of the proposed drug substance and drug product.

The above recommendation is supported by the approval recommendation that was made for this NDA by the product quality microbiology reviewer (Dr. Bryan S. Riley). The microbiology review # 2 dated April 16, 2008 includes a recommendation that a Phase 4 commitment from the applicant regarding establishing an endotoxin specification be accepted as a condition of approval.

The current chemistry review is a follow-up review to Chemistry Review # 1 and includes a review of information provided in the amendments dated March 11, 2008 and April 16, 2008.

### **Amendments dated March 11, 2008 and April 14, 2008**

The amendment dated March 11, 2008 contains the applicant's responses to the Agency's comments listed in the Chemistry Review # 1 (forwarded to the applicant on February 12, 2008).

The following comments were forwarded to the applicant via fax dated February 12, 2008:

1. Please confirm that the container/closure system (including inks) proposed for the current bimatoprost formulation (0.01%) is the same as the one for the approved NDA 21-275 (please provide the date of approval of the (b) (4) bottles for Lumigan™). Please provide a head-to-head comparison of the container closure systems (components, sizes, fill volumes and materials, including inks) for the two products.
2. Please provide information regarding the safety and acceptability of the inks to be used in the marketed container/closure system for the proposed drug product. Confirm that the extractable studies were conducted on the finished container/closure system (i.e. using all the proposed inks) and no extractables were derived from the inks to be used for the commercial containers. Also, confirm that that no secondary packaging-related leachables have been detected in the proposed bimatoprost drug product (0.01%).
3. Please note that in your Batch Release Analysis Summary (Table 3.2.P.5.4-2) the acceptance criteria and test results for benzalkonium chloride assay reported for lots 12000, 12001, and 12002 do not correspond to the level of benzalkonium chloride (200 ppm BAK) declared for each of these lots in the second row of the table (Dosage Strength). Please clarify.

4. Please provide updated stability data for the drug product. Please include the most updated results of the weight loss, which appear particularly excessive for the 1 mL and 2.5 mL fill samples. Note that the expiration dating will be based on the available and acceptable stability information including the amount of data generated up to date.

**Comment 1**

Please confirm that the container/closure system (including inks) proposed for the current bimatoprost formulation (0.01%) is the same as the one for the approved NDA 21-275 (please provide the date of approval of the (b) (4) bottles for Lumigan™). Please provide a head-to-head comparison of the container closure systems (components, sizes, fill volumes and materials, including inks) for the two products.

In response to Comment 1, the applicant stated that the container/closure system (bottle, tip, and cap) proposed for the 0.01% Bimatoprost/200 ppm BAK Ophthalmic Solution is Allergan’s standard container closure configuration for ophthalmic solutions. This configuration, referred to as (b) (4), is the same as that used for LUMIGAN® (Bimatoprost 0.03%). The applicant provided Table 1 (reproduced below) for the comparison of all components of the container/closure systems, including fill volumes, adhesive, and inks, between the two products. The label inks for the 0.01% Bimatoprost/200 ppm BAK Ophthalmic Solution include different inks (from same supplier, (b) (4)) when compared to those of LUMIGAN®. Also, a different (b) (4) adhesive (from same supplier, (b) (4)) is used in the label for 0.01% Bimatoprost/200 ppm BAK Ophthalmic Solution. However, the applicant stated that the inks and the adhesive have been proven to be acceptable in the leachables studies conducted on the finished product (response to Comment 2).

**Table 1 Comparison of Container Closure Configurations for 0.01% Bimatoprost / 200 ppm BAK Ophthalmic Solution and LUMIGAN®**

Product	LUMIGAN® (Bimatoprost 0.03%)		0.01% Bimatoprost / 200 ppm BAK Ophthalmic Solution	
<b>Fill Volumes</b>	1 mL, 2.5 mL, (b) (4)	5 mL, 7.5 mL	1 mL, 2.5 mL	5 mL, 7.5 mL
<b>Bottle<sup>1</sup></b>	5-mL (b) (4) Bottle, (b) (4) LDPE <sup>2</sup> , White	10-mL (b) (4) Bottle, (b) (4) LDPE, White	5-mL (b) (4) Bottle, (b) (4) LDPE, White	10-mL (b) (4) Bottle, (b) (4) LDPE, White
<b>Tip<sup>1</sup></b>	(b) (4) LDPE, White			
<b>Cap<sup>1</sup></b>	(b) (4) Turquoise	(b) (4) Turquoise	(b) (4) Turquoise	(b) (4) Turquoise
<b>Label Inks<sup>4</sup></b>	(b) (4) inks. (b) (4) inks. (b) (4) inks <sup>5</sup> (b) (4) inks <sup>5</sup>			
<b>Label Adhesive<sup>4</sup></b>	(b) (4) adhesive. adhesive. adhesive. adhesive.			

<sup>1</sup> Bottles, tips, and caps are manufactured by Allergan Inc.

<sup>2</sup> Low density polyethylene (b) (4)

<sup>3</sup> High impact polystyrene (b) (4)

<sup>4</sup> Labels are manufactured by (b) (4)

<sup>5</sup> Proprietary information from (b) (4) of the submitted NDA 22-184/0000

In response to the comment regarding the approval of the (b) (4) bottle for LUMIGAN®, the applicant stated that the 1 mL fill size (physician sample) of LUMIGAN® in the 5 mL (b) (4) bottle was approved under NDA 21-275 in Supplement S-008 on June 4, 2003 while the 2.5 mL fill size of LUMIGAN® in the 5 mL (b) (4) bottle was approved under NDA 21-275 in Supplement S-010/S-012 on August 25, 2003.

Comments:

The above information (approval of (b) (4) bottles for LUMIGAN) was verified in DFS and found correct.

Regarding the container/closure system comparison, the only difference between the containers used for LUMIGAN and the proposed drug product is the adhesive ( (b) (4) ) and some of the inks. However, the adhesive is supplied from the same manufacturer as that used for LUMIGAN. As stated in review # 1, the applicant has provided acceptable information regarding the adhesive, including documentation from its manufacturer stating that (b) (4) adhesive meets Food Additive Regulation 21 CFR 175.105. Similarly, the inks used for the proposed product are of the same series and by the same manufacturer ( (b) (4) ) as those used for LUMIGAN (some are identical); in addition, some of their components are similar. Finally, the results of extractable studies showing no extractables above 1 ppm further support their use for the proposed product. It should also be noted that the secondary packaging system (unit cartons supplied by (b) (4) ) is the same for both products (as stated in the stability section 2.3. P.8 of the March 11, 2008 amendment). The response is acceptable.

Comment 2

*Please provide information regarding the safety and acceptability of the inks to be used in the marketed container/closure system for the proposed drug product. Confirm that the extractable studies were conducted on the finished container/closure system (i.e. using all the proposed inks) and no extractables were derived from the inks to be used for the commercial containers. Also, confirm that that no secondary packaging-related leachables have been detected in the proposed bimatoprost drug product (0.01%).*

*In response to Comment 2, the applicant stated that Allergan tested the proposed commercial primary and secondary packaging (printed unit carton and printed test insert) components including proposed inks as part of the registration stability studies. Leachable studies were conducted on the finished container/closure system and compared to leachable control samples consisting of glass ampoules, unlabeled bottles, and unlabeled bottles in the unit carton. The applicant stated that no trendable leachables were found above 1 ppm attributable to the proposed packaging components (NDA 22-184/0000, Section 3.2.P.8.1). The applicant further stated that all packaging components including inks are safe and acceptable based on toxicology and safety*

evaluations (NDA 22-184/0000 Att 3.2.P.8.1-7 Proposed Leachables Justification Memo). Therefore, Allergan considers the complete packaging system for Bimatoprost 0.01%/200 ppm BAK Ophthalmic Solution to be safe and acceptable.

Comments:

The response is acceptable.

As discussed in review # 1, the applicant had proposed the acceptance criteria for leachables for the current product in the following manner. There are separate acceptance criteria proposed for  (b) (4). Other leachables are proposed to be controlled via two categories “Other Specified Leachables” and “Unspecified Leachables”. The applicant stated that this leachable category reporting approach allows Allergan to continue to monitor product for presence of leachables while focusing on the more significant leachable impurities.

It should be noted that the specification comparison table provided in review # 1 contained the acceptance criteria for leachable impurities approved for LUMIGAN (bimatoprost ophthalmic solution), 0.03%, via the original NDA 21-275. However, the acceptance criteria for leachables were somewhat revised via subsequent supplements to NDA 21-275. Therefore, the table below reflects the current approved acceptance criteria for impurities and leachables (approved via NDA 21-275/S-009) as compared to the acceptance criteria for impurities and leachables proposed for the current product.

NDA 21-275/S-009 vs. NDA 22-184:



(b) (4)



\* approved via S-018; \*\* approved via S-019

As seen above, the proposed acceptance criteria for leachables for the current product differ slightly from those approved for LUMIGAN (although they are very close). As discussed in review # 1, the applicant stated that this proposed leachable specification is supported by ICH total daily intake and no-effect toxicology guidance for impurities (3.2.P.8.1-7 Proposed Leachables Justification Memo). The calculation provided in this memo estimated that with the Total Daily Intake (TDI) of the formulation <sup>(b) (4)</sup> the maximum exposure of other specified leachables would be <sup>(b) (4)</sup> (based on the allowable 0.3 µg/day for any unknown genotoxic impurity).

The approach taken by the applicant for establishing the acceptance criteria for leachables in the proposed drug product appears quite conservative. The applicant used the allowable limit for genotoxic and carcinogenic impurities <sup>(b) (4)</sup>



It should be noted that the similar limit ( (b) (4) ) was recently found acceptable and approved (using the same approach) for the leachables (b) (4) found in LUMIGAN® (supplement NDA 21-275/SCS-019 approved March 25, 2008). It should also be noted that only some of the leachables found in LUMIGAN were observed in stability testing of the currently proposed drug product at the very low levels. The analytical procedures used for leachable testing for both products are identical. That includes a (b) (4) in the current product that was also approved for LUMIGAN via supplement NDA 21-275/SCS-017 (replacing the previous procedure AP-G063).

The response is acceptable.

### **Comment 3**

*Please note that in your Batch Release Analysis Summary (Table 3.2.P.5.4-2) the acceptance criteria and test results for benzalkonium chloride assay reported for lots 12000, 12001, and 12002 do not correspond to the level of benzalkonium chloride (200 ppm BAK) declared for each of these lots in the second row of the table (Dosage Strength). Please clarify.*

*In response to Comment 3, the applicant stated that the levels of benzalkonium chloride were incorrectly declared in the dosage strength description. The correct benzalkonium chloride concentration for lots 12000, 12001 and 12002 is 50 ppm and test results for these lots met acceptance criteria. Table 3.2.P.5.4-2 Batch Release Analysis Summary has been updated to reflect the correct benzalkonium chloride levels. In addition, a similar correction was made for lot 12000 in Table 3.2.P.5.4-1 Complete Listing of All Lots of Bimatoprost Drug Product.*

### **Comment:**

The corrected tables were resubmitted. The response is acceptable.

### **Comment 4**

*Please provide updated stability data for the drug product. Please include the most updated results of the weight loss, which appear particularly excessive for the 1 mL and 2.5 mL fill samples. Note that the expiration dating will be based on the available and acceptable stability information including the amount of data generated up to date.*

*In response to Comment 4, the applicant provided a stability update, which includes an interim stability summary report containing cumulative data through 18 months at 25°C/40%RH provided in section 3.2.P.8.3-1 (Report PA-2007-274 18-Month Interim Stability Report For Primary Stability Batches of 0.01% Bimatoprost 200 ppm BAK Ophthalmic Solution (9668X)).*

Stability batches 40444, 40558, and 42395 were packaged into 1 mL/5-mL, 2.5 mL/5-mL, (b) (4) mL/5-mL, 5 mL/10-mL and 7.5 mL/10-mL fill volume/fill capacity configurations.

Batch 40444 is comprised of sublots 40079 (1 mL/5-mL), 40084 (2.5 mL/5-mL), (b) (4) 40080 (5 mL/10-mL), and 40081 (7.5 mL/10-mL).

Batch 40558 is comprised of sublots 40653 (1 mL/5-mL), 40652 (2.5 mL/5-mL), (b) (4)  
40649 (5 mL/10-mL), and 40648 (7.5 mL/10-mL).

Batch 42395 is comprised of sublots 42552 (1 mL/5-mL), 42551 (2.5 mL/5-mL), (b) (4)  
42553 (5 mL/10-mL), and 42550 (7.5 mL/10-mL).

The proposed commercial fill sizes are 2.5 mL and (b) (4) in a 5-mL bottle, and 5 mL and 7.5-mL in a 10-mL bottle and 1 mL fill in a 5-mL bottle for the physician sample.

All primary stability batches have been studied for bimatoprost potency, bimatoprost impurities, benzalkonium chloride, leachable impurities, physical appearance, pH, osmolality, sterility, antimicrobial preservative effectiveness, particulate matter, and weight loss.

The applicant stated that bimatoprost potency was found to be the stability limiting parameter, due to water loss, for the determination of the expiry dating. Under refrigerated conditions, there is no stability limiting parameter for the product.

Based on the evaluation of up to 18 months of refrigerated ( $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ ) and room temperature ( $25^{\circ}\text{C}/40\% \text{ RH}$ ) and 6 months of accelerated data ( $40^{\circ}\text{C}/\text{NMT } 25\% \text{ RH}$ ), the applicant has proposed a 24-month expiration dating for the product packaged in the 2.5 mL, 5 mL, and 7.5 mL fill configurations and 12 months for the 1 mL fill configuration with a storage statement of  $2^{\circ} - 25^{\circ}\text{C}$  ( $36^{\circ} - 77^{\circ}\text{F}$ ). In addition to the stability testing, the applicant has conducted some statistical evaluation in support of the proposed expiration dating for 2.5 mL, 5 mL, and 7.5 mL fill configurations.

Comments:

In the analysis of stability data, no significant difference was observed for samples stored at  $25^{\circ}\text{C}/40\% \text{ RH}$  or  $40^{\circ}\text{C}/\text{NMT } 25\% \text{ RH}$  due to package orientation. The results of the photo-stress study, such as bimatoprost potency values remained within specification. No significant changes in related substances levels were observed. Also, the results for freeze/thaw cycling samples remain within the proposed product shelf specifications and all results for the freeze/thaw study are comparable to the control. In addition, the results for low/high temperature samples remain within the proposed product shelf specifications and were comparable to the control.

The major trend observed in the long term and accelerated stability studies includes the weight loss increase; especially for the smaller volume samples (1 mL and 2.5 mL fill volumes). Because of the increases in weight loss, other parameters such as: bimatoprost assay, benzalkonium chloride assay and osmolality were also affected for lower volume samples. However, the results of these tests remain within the proposed acceptance criteria for all samples stored under the long term conditions. In addition, no significant changes were observed for any other parameters (including degradation products) tested in stability studies. The stability results indicate that the proposed drug product packaged in the proposed container/closure system is relatively stable.

The results of weight loss, bimatoprost assay, benzalkonium chloride assay and osmolality for samples of all packaging configurations tested and stored at different storage conditions are outlined below.

Comment:

The amount of benzalkonium chloride in the drug product should be stated on the bottle label. The following revision should be made in the bottle labels (all fill volumes), to read:

Preservative: Benzalkonium chloride 0.2 mg/mL

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/s/

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Dorota Matecka  
4/17/2008 02:42:08 PM  
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Norman Schmuiff  
4/18/2008 08:50:56 AM  
CHEMIST

**NDA 22-184**

**LUMIGAN RC\***  
**(bimatoprost ophthalmic solution), 0.01%**

**Allergan, Inc.**

**Dorota Matecka**

**Division of Pre-Marketing Assessment II, Branch IV**  
**ONDQA**

\* trade name currently proposed and under evaluation

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# Chemistry Review Data Sheet

1. NDA 22-184
2. REVIEW # 1
3. REVIEW DATE: 03-Mar-2008
4. REVIEWER: Dorota Matecka
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original submission	02-Jul-2007
BC	23-Aug-2007
IR	12-Feb-2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	2-Jul-2007
BC	23-Aug-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Allergan, Inc.
Address:	2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534
Representative:	Paul Stone, PhD, Director, Regulatory Affairs
Telephone:	714-246-4272

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: LUMIGAN RC
- b) Non-Proprietary Name (USAN): bimatoprost ophthalmic solution
- c) Code Name/# (ONDC only): AGN 192024
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

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

## 10. PHARMACOL. CATEGORY: Ophthalmic

## 11. DOSAGE FORM: Solution

## 12. STRENGTH/POTENCY: 0.01%

## 13. ROUTE OF ADMINISTRATION: Topical/ocular

14. Rx/OTC DISPENSED:  Rx      OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

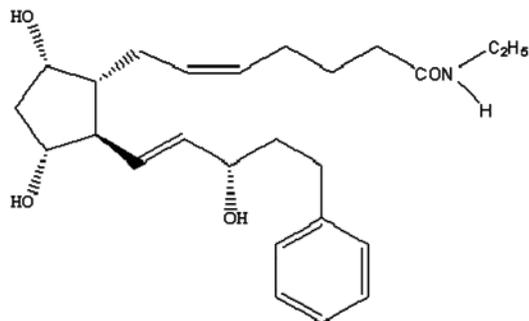
Not a SPOTS product

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

(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-N-ethyl-5-heptenamide

## Chemistry Review Data Sheet

Figure 3.2.S.1.2-1 Structural Formula of Bimatoprost

 $C_{25}H_{37}NO_4$ 

MW = 415.58

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		
2461	III	Allergan Sales, LLC	(b) (4)	4	N/A		
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		

<sup>1</sup> 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")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

## B. Other Documents: NDA 21-275 (Allergan)

## Chemistry Review Data Sheet

## 18. STATUS:

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMETS	Pending		
EA	N/A (request for a categorical exclusion)	N/A	
Microbiology	Approvable	04-Feb-2008	Bryan S. Riley, Ph.D.

# The Chemistry Review for NDA 22-048

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is currently recommended for an approvable action. There are several comments listed in the end of this review that need to be addressed by the applicant (previously forwarded to the applicant). Also, the product quality microbiology review recommended an approvable action of this NDA (review conducted by Dr. Bryan S. Riley dated 04-Feb-2008). The labeling review is pending (including the proposed trade name: LUMIGAN RC). In addition, the overall compliance recommendation has not been yet completed by the Office of Compliance for this NDA.

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

N/A

### II. Summary of Chemistry Assessments

The original NDA was submitted for the treatment of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension. This is a new formulation of bimatoprost, which is the active ingredient of LUMIGAN<sup>®</sup> (bimatoprost ophthalmic solution) 0.03%, which has been marketed in the US under NDA 21-275 since March 2001.

The proposed indication for the current product is the same as that for LUMIGAN<sup>®</sup>. Compared with LUMIGAN, which contains 0.03% bimatoprost and 50 ppm benzalkonium chloride (BAK), the current product contains a third of the concentration of bimatoprost (0.01%) and 200 ppm BAK. The applicant claims that the current product with a reduced concentration of bimatoprost achieves equivalent IOP-lowering efficacy to LUMIGAN<sup>®</sup> and an improved safety profile.

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

The 0.01% Bimatoprost/200 ppm BAK Ophthalmic Solution was developed from the LUMIGAN<sup>®</sup> product platform with modifications to the levels of the drug substance, bimatoprost, the preservative, benzalkonium chloride, and the tonicity agent, sodium chloride. No new ingredients have been added. LUMIGAN<sup>®</sup> is manufactured by Allergan under approved NDA 21-275.

As with LUMIGAN<sup>®</sup>, the proposed drug product is a clear, colorless, isotonic, sterile solution containing 0.01% (w/v) bimatoprost as the active ingredient and 0.02% (w/v) benzalkonium chloride as the preservative. The inactive ingredients include sodium chloride, dibasic sodium phosphate (b)(4), citric acid (b)(4), and purified water. The solution pH is

## Executive Summary Section

adjusted to (b) (4) using either (b) (4) sodium hydroxide or (b) (4) hydrochloric acid. Except for the drug substance, all ingredients are USP/Ph Eur, NF/Ph Eur or USP compendial grade materials.

The 0.01% Bimatoprost/200 ppm BAK Ophthalmic Solution manufacturing process involves (b) (4)

Bimatoprost is a synthetic prostamide analogue with ocular hypotensive activity. Bimatoprost drug substance to be used in the proposed formulation (0.01% Bimatoprost/200 ppm BAK Ophthalmic Solution) is the same drug substance submitted and approved via the original NDA 21-275 for LUMIGAN<sup>®</sup> (bimatoprost ophthalmic solution, 0.03%). Therefore, for the chemistry, manufacturing, and controls (CMC) information for the bimatoprost drug substance, the reference is made to the NDA 21-275.

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

The proposed drug product is indicated for the (b) (4) of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

The primary container/closure system for the drug product consists of a multiple-dose bottle and tip manufactured of low density polyethylene (LDPE, (b) (4)) and a cap manufactured of (b) (4) polystyrene (b) (4). The bottles and tips are colored white (b) (4)

. The caps are colored turquoise (b) (4)  
. Bottles and tips are (b) (4)  
. Caps are (b) (4). The finished product is labeled with a (b) (4). The tamper evident security feature for the primary packaging container is (b) (4).

The planned market configurations include a 1 mL fill in a 5-mL bottle for the physician sample, a 2.5 mL fill in a 5-mL bottle, and a 5 mL and 7.5 mL fill in a 10-mL bottle. The secondary packaging consists of a unit cardboard carton and an insert.

The currently proposed expiration dating a 24-month expiration date for 0.01% Bimatoprost/200 ppm BAK Ophthalmic Solution (9668X) in the 2.5 mL, 5 mL, and 7.5 mL proposed fill configurations and a 12-month expiration date for the 1 mL proposed fill configuration when stored at 2° - 25°C (36° - 77°F). The proposed expiration dating and storage conditions will be evaluated when the next stability update is submitted.

**C. Basis for Approvability or Not-Approval Recommendation**

The original application contains mostly adequate information regarding the quality of the drug substance and the drug product. However, there are several issues pending resolution, such as stability of the proposed formulation packaged in the proposed container/closure system, specifically loss on drying, which appears relatively excessive, particularly for low volume samples. Several comments regarding the proposed container closure system, batch analysis

## Executive Summary Section

summary, and stability of the proposed drug product (listed in the end of this review) have been previously forwarded to the applicant and need to be addressed. The proposed container closure system, drug product specification, stability and the proposed expiration dating will be re-evaluated via review # 2 when the response to the Agency' comments is provided.

The product quality microbiology review recommended an approvable action of this NDA from the microbiology viewpoint (review dated 04-Feb-2008) and their recommendation included an addition of endotoxins test and acceptance criteria in the drug product specification.

The review of the labeling and the container labels is pending (including the proposed trade name: LUMIGAN RC).

Bimatoprost drug substance is manufactured by [REDACTED] (b) (4)

Upon approval, the drug product will be manufactured and marketed by Allergan. However, an overall compliance recommendation for this NDA from the Office of Compliance is currently pending.

### III. Administrative

#### A. Reviewer's Signature

DFS

#### B. Endorsement Block

Chemist/DMatecka/Date: Same date as draft review  
ChemistryTeamLeader/NSchmuff  
ProjectManager/MPuglisi

#### C. CC Block

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Dorota Matecka  
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Norman Schmuiff  
3/14/2008 12:07:23 PM  
CHEMIST

Initial Quality Assessment  
Branch   IV    
Pre-Marketing Assessment Division   II  

**OND Division:** Division of Anti-Infective and Ophthalmology Products  
**NDA:** 22-184  
**Applicant:** Allergan  
**Stamp Date:** June 14, 2007  
**PDUFA Date:** April 15, 2008  
**Trademark:** None requested  
**Established Name:** Bimatoprost ophthalmic solution  
**Dosage Form:** Ophthalmic Solution 0.01%  
**Route of Administration:** Topical ophthalmic  
**Indication:** Reduction of elevated intraocular pressure

**PAL:** Linda Ng, Ph.D.

	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

## Summary and Critical Issues:

### Summary

In general, this NDA, 5S, dated June 14, 2007, is straightforward. Bimatoprost Ophthalmic Solution, 0.01% is a reduced strength of Lumigan, NDA 21-275, manufactured by the same firm, Allergan. This product contains 0.01% of bimatoprost instead of the 0.03%. The new formulation is modified to enhance absorption, claimed to have (b) (4). Both products will be marketed with the same indication, i.e., reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. This is a 505(b)(2) NDA, Quality submitted in CTD format and preclinical and clinical in eCTD format. NDA 22-184 has been accepted as a standard NDA.

Bimatoprost is manufactured by (b) (4). The drug product is manufactured at the Allergan's Waco, Texas facility.

The product formulation contains an increased amount of benzylalkonium chloride and reduced amount of sodium chloride compared to Lumigan. Target pH of solution product is (b) (4).

Testing, 2.3.S.2.1, for release and stability of the bimatoprost is at Allergan at Waco, Texas and at Westport, Ireland sites. Testing, 2.3.P.3.1, for drug product release is at Waco, Texas and for stability at the Westport, Ireland.

The container closure is (b) (4) white polyethylene bottle fitted with a white polyethylene dispensing plug and turquoise polypropylene cap. The bottle and plug are sterilized by (b) (4) and the cap by (b) (4).

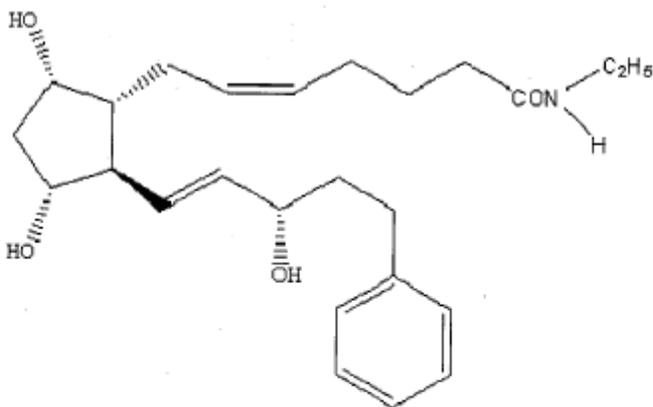
(b) (4). The bottle size is different from Lumigan's 8 mL. The drug product, available in 1 mL, 2.5 mL, (b) (4) fill in 5 mL bottle, and 5 mL and 10 mL fill in 10 mL bottle, is manufactured sterile by Allergan Inc, Waco, Texas. The mean dosage drop size is (b) (4).

Stability data are provided for three batches of the drug product at the commercial manufacturing site, Waco, Texas with 12 months for two batches and 9 months for one batch.

Allergan claimed a categorical exclusion from preparing an environmental assessment – section 1.12.14.

A microbiology consult was submitted by the OND PM, Michael Puglisi and Dr. Brian Riley is the microbiologist assigned. Mr. Puglisi submitted the labeling consult to DDMAC on July 17, 2007 but did not submit any request to DMETS since the firm did not propose a trade name. An EES request was submitted by Linda Athey, ONDQA PM on August 17 2007.

Structure and properties of the drug substance are listed:



Molecular Formula

C<sub>25</sub>H<sub>37</sub>NO<sub>4</sub>

Relative Molecular Mass

415.58

***Critical issues for review***

- The typical developmental studies like freeze-thaw cycling, drop size evaluation, leachables evaluation, water loss evaluation have been performed. Quality of data will be evaluated by reviewer.
- The amount and type of stability data with statistical evaluation appeared adequate and reviewer will evaluate quality.
- A trade name was not proposed and the OND PM did not submit a DMETS consult.
- Overall, no glaring issue could be found from a brief perusal of the NDA

- **Comments for 74-Day Letter**

None recommended.

**D. Review, Comments and Recommendation:**

The NDA is acceptable for filing. No team review is recommended. A single reviewer can review this NDA due to the fairly straightforward issues. Dr. Dorota Matecka has been assigned to review the NDA.

\_\_\_\_Linda Ng, Ph.D.\_\_\_\_\_  
Pharmaceutical Assessment Lead

\_\_\_\_September 5, 2007\_\_\_\_\_  
Date

\_\_\_\_Elaine Morefield, Ph.D.\_\_\_\_\_  
Director

\_\_\_\_\_  
Date

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Linda Ng  
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Elaine Morefield  
9/5/2007 05:16:13 PM  
CHEMIST

**NDA FILEABILITY CHECKLIST**

**NDA Number: 22-184**

**Applicant: Allergan Inc, 2525 Dupont Drive, Irvine, CA 19534**

**Letter Date: July 2, 2007**

**Stamp Date: July 3, 2007**

**Drug Name: Bimatoprost Ophthalmic Solution, 0.01%**

**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		
3	On its face, is the section legible?	Y		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	Y		
5	Is a statement provided that all facilities are ready for GMP inspection?		N	Implied but not stated
6	Has an environmental assessment report or categorical exclusion been provided?	Y		Exemption requested; no calculation provided. M.1.12.5
7	Does the section contain controls for the drug substance?	Y		Bimatoprost from (b) (4), (b) (4). Reference to NDA 21-275
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 in 5 and 10 mL bottles. 3 batches: 2 batches for 12 months and 1 batch for 9 months
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	Y		
11	Have draft container labels been provided?	Y		
12	Has the draft package insert been provided?	Y		
13	Has an investigational formulations section been provided?		N	None detected. This is a reduced strength of an approved drug product.
14	Is there a Methods Validation package?	Y		Located in Regional Information
15	Is a separate microbiological section included?	Y		

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Chemistry Reviewer:

Dorota Matecka, Ph.D.

Pharmaceutical Assessment Lead:

Linda Ng, Ph.D.

Branch Chief:

Norman Schmuft, Ph.D.

Prepared by: LNg 8/8/07

Letters of Authorizations (LOA) provided for three Type III DMFs in M.1.4.1. for DMF (b) (4) DMF (b) (4) and DMF (b) (4).

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