CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-804 (formerly 21-675)

Administrative/Correspondence Reviews

Section III Patent Certification and Statement Concerning Patented Indication

Enclosed in this section are statements of patent certification of Bausch & Lomb Incorporated's 505(b)(2) application for Zylet®. Also enclosed are the statements concerning the required notices to patent owners(s) and NDA holders.

These statements are in accord with the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1984, and with the final regulations effective November 2 1994.

Patent Certification

Paragraph II Certification

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended, September 24, 1984, and with the final regulations effective November 2, 1994, Patent Certification is hereby provided for our 505(b)(2) application for Zylet®.

Bausch & Lomb Incorporated, hereby certifies that, in its opinion and to the best of its knowledge, U.S. Patent No. 3,691,279 covering the active ingredient Tobramycin expired September 12, 1989. This certification is made in accordance with Section 505(b)(2)(A) of Title 1 of the FD&C Act, as amended September 24, 1984, and pursuant to 21 CFR 314.50(i)(1)(i)(A).

Bausch & Lomb Incorporated

Patent Certification

Paragraph IV Certification
Licensing Agreement

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended, September 24, 1984, and with the final regulations effective November 2, 1994, Patent Certification is hereby provided for our 505(b)(2) application for Zylet®.

Bausch & Lomb Incorporated has been granted a patent license by Nicholas Bodor, the owner of U.S. Patent No. 4,996,335. This notice will be sent by certified mail, return receipt requested to Dr. Bodor.

Bausch & Lomb Incorporated

1.1 Patent Information
1.1.1 Market Exclusivity Statement

Claimed Exclusivity under 21 CFR § 314.108(b)(4)

Pursuant to 21 CFR 314.50(j), Bausch & Lomb hereby claims that the drug product subject of this application is entitled to three (3) years of market exclusivity from the date of approval of this application.

New clinical investigations

In accordance with 21 CFR 314.108(b)(4), Bausch & Lomb certifies that to the best of the applicant's knowledge each of the clinical investigations included in this application meets the definition of "new clinical investigations" set forth in 21 CFR 314.108(a). The clinical investigation(s) included in this application have not been previously submitted to the FDA and thus have not been relied on by the FDA to demonstrate substantial evidence of safety or efficacy of a previously approved drug product.

Essential to approval

The clinical investigation(s) included in this application are essential to approval of LET because the applicant has thoroughtly searched the scientific literature and, to the best of the applicant's knowledge, there is no other data available that could support the approval of this application because there is no other available evidence of the safety and efficacy of this particular drug product.

Conducted or sponsored by

These clinical investigations were conducted or sponsored by Bausch & Lomb under IND 36,209.

Bausch & Lomb Incorporated

ATTESTATION UNDER 21 CFR §314.53(c)(iv)(2)

The undersigned declares that Patent No. 4,996,335 covers the formulation, composition, and/or method of use of ZYLET. This product is the subject of this application for which approval is being sought.

By: 

Glenn D. Smith
Assistant Counsel
Bausch & Lomb Incorporated

ATTESTATION UNDER 21 CFR §314.53(c)(iv)(2)

The undersigned declares that Patent No. 5,540,930 covers the formulation, composition, and/or method of use of ZYLET. This product is the subject of this application for which approval is being sought.

By: 

Glenn D. Smith
Assistant Counsel
Bausch & Lomb Incorporated

ATTESTATION UNDER 21 CFR §314.53(c)(iv)(2)

The undersigned declares that Patent No. 5,747,061 covers the formulation, composition, and/or method of use of ZYLET. This product is the subject of this application for which approval is being sought.

By: 

Glenn D. Smith
Assistant Counsel
Bausch & Lomb Incorporated

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER 21-675

NAME OF APPLICANT / NDA HOLDER
Bausch & Lomb Incorporated

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Zylet

ACTIVE INGREDIENT(S)	STRENGTH(S)
Loteprednol etabonate	0.5%
Tobramycin	0.3%

DOSAGE FORM
Suspension / Drops

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
4,996,335	February 26, 1991	03/09/2012

d. Name of Patent Owner	Address *(of Patent Owner)*	FAX Number *(if available)*
Nicholas Bodor, Ph.D, D.Sc.	10101 Collins Ave. #4A	
	City/State: Bal Harbour, FL	
	ZIP Code: 33154	
	Telephone Number: (305) 575-6028	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	FAX Number *(if available)*
	City/State	
	ZIP Code	
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

FORM FDA 3542a (7/03)

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☒ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2 Claim Number (*as listed in the patent*)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
90	☒ Yes	☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*

Zylet is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

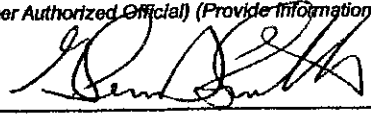
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	August 20, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: Glenn D. Smith	
Address: 1 Bausch & Lomb Place	City/State: Rochester, NY
ZIP Code: 14604	Telephone Number: (585) 338-6142
FAX Number *(if available)*: (585) 338-8706	E-Mail Address *(if available)*: glenn_smith@bausch.com

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER 21-675

NAME OF APPLICANT / NDA HOLDER
Bausch & Lomb Incorporated

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Zylet

ACTIVE INGREDIENT(S)	STRENGTH(S)
Loteprednol etabonate	0.5%
Tobramycin	0.3%

DOSAGE FORM Suspension / Drops

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,747,061	May 5, 1998	10/25/13

d. Name of Patent Owner
Bausch & Lomb Incorporated

Address *(of Patent Owner)*
1 Bausch & Lomb Place

City/State Rochester, NY

ZIP Code 14604

FAX Number *(if available)* (585) 338-8706

Telephone Number

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to *receive notice of patent certification* under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code

FAX Number *(if available)*

Telephone Number

E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Claim Number (*as listed in the patent*): 18, 19 (Claim 19 is is dependent upon Claim 18.) — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*

Zylet is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	August 20, 2003

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Check applicable box and provide information below.

☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: Glenn D. Smith	
Address: 1 Bausch & Lomb Place	City/State: Rochester, NY
ZIP Code: 14604	Telephone Number: (585) 338-6142
FAX Number *(if available)*: (585) 338-8706	E-Mail Address *(if available)*: glenn_smith@bausch.com

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
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See OMB Statement on Page 3.

NDA NUMBER 21-675

NAME OF APPLICANT / NDA HOLDER
Bausch & Lomb Incorporated

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Zylet

ACTIVE INGREDIENT(S)	STRENGTH(S)
Loteprednol etabonate	0.5%
Tobramycin	0.3%

DOSAGE FORM Suspension / Drops

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,540,930	July 30, 1996	October 25, 2013

d. Name of Patent Owner	Address *(of Patent Owner)*	
Bausch & Lomb Incorporated	1 Bausch & Lomb Place	
	City/State Rochester, NY	
	ZIP Code 14604	FAX Number *(if available)* (585) 338-8706
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☐ Yes	☒ No
4.2 Claim Number (*as listed in the patent*)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	August 20, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: Glenn D. Smith	
Address: 1 Bausch & Lomb Place	City/State: Rochester, NY
ZIP Code: 14604	Telephone Number: (585) 338-6142
FAX Number *(if available)*: (585) 338-8706	E-Mail Address *(if available)*: glenn_smith@bausch.com

EXCLUSIVITY SUMMARY FOR NDA # **50-804** SUPPL #_____

Trade Name **ZYLET** Generic Name **loteprednol etabonate and tobramycin ophthalmic suspension, 0.5%/0.3%**

Applicant Name **Bausch & Lomb** **HFD-550**

Approval Date If Known **December 14, 2004**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /**XX**/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /___/ NO /**XX**/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The study was designed and performed as a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_**XX**_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_**XX**_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /**XX**/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other

than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___ / NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /**XX**/ NO /___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#**20-583 loteprednol etabonate**

NDA#**20-803 loteprednol etabonate**

NDA#**50-541 tobramycin**

ANDA#**64-052 tobramycin**

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered ``NO'' for original approvals of new molecular entities.) IF ``YES'' GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This

section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_**XX**_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product

and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency

to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are

there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature _____ Date _12/14/2004__
Lucious Lim, M.D.
Clinical Reviewer

Signature _____ MD Date _12/14/2004__
Wiley A. Chambers, M.D.
Deputy Director

Form OGD-011347 Revised 05/10/2004

cc:
Archival NDA ~~21-675~~ 50-804
HFD-550 /Division File
HFD-550 /RPM / RodriguezR
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 50-804 Supplement Type (e.g. SE-4, SE5): ____ Supplement Number: _____

mp Date: September 8, 2003 Action Date: December 14, 2004

HFD 550 Trade and generic names/dosage form: Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) 0.5%/0.3%

Applicant: Bausch & Lomb Therapeutic Class: Ophthalmic – Corticosteroid/Anti-Infective Combination

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

XX No: Please check all that apply: ___Partial Waiver XX Deferred ___Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

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Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

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- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children

- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

~~Age/weight range being deferred:~~ ~~12/7/2004~~ **Sponsor has agreed to study 60 patients ages 0-6 years old.**

Min _____	kg_____	mo._____	yr.__0___	Tanner Stage_____
Max_____	kg_____	mo._____	yr.__6___	Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other:_____

Date studies are due (mm/dd/yy): ~~December 7, 2006~~ March 31, 2007

If studies are completed, proceed to Section D Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: Lucious Lim, M.D._____ Clinical Reviewer

Raphael R.Rodriguez _____ RPM

cc: NDA 50-804
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

1.4 Debarment Certification (Section 16)

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, Bausch & Lomb certifies that it did not and will not use in any capacity in connection with this application the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or 306(b) of the Act.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached for listing of all investigators in covered studies.	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Brian Levy, O.D., M.Sc.	Vice President, Medical and Clinical Affairs
FIRM / ORGANIZATION: Bausch & Lomb, Inc.	
SIGNATURE	DATE: 8/14/03

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

1.7 Financial Disclosure Statement (Section 19)

Listing of all investigators in covered studies (attachment to Form FDA 3454).

Study Number	Investigator Name
BLP 358-003	David A. Shulman, M.D.
BLP 358-003	Subinvestigator: [redacted]
BLP 358-004	Jack V. Greiner, O.D., D.O., Ph.D.
BLP 358-004	Subinvestigator: [redacted]
BLP 358-004	Subinvestigator: [redacted]
BLP 358-004	Subinvestigator: [redacted]
BLP 358-004	Subinvestigator: [redacted]
BLP 358-004	Subinvestigator: [redacted]
BLP 358-004	Subinvestigator: [redacted]
BLP 358-004	Subinvestigator: [redacted]
BLP 358-005	Thomas R. Walters, M.D.
BLP 358-005	Gregory L. Henderson, M.D.
BLP 358-006	Donald E. Beahm, MD
BLP 358-006	Bruce Bodner, MD
BLP 358-006	Subinvestigator: [redacted]
BLP 358-006	Subinvestigator: [redacted]
BLP 358-006	E. Britt Brockman, MD
BLP 358-006	Todd A. Brockman, MD
BLP 358-006	David Cooke, MD
BLP 358-006	Subinvestigator: [redacted]
BLP 358-006	Subinvestigator: [redacted]
BLP 358-006	Lawrence Raymond DeBarge, MD
BLP 358-006	Matthew Ehrlich, MD
BLP 358-006	Jonathan M. Frantz MD, F.A.C.S.
BLP 358-006	Walter I. Fried, Ph.D., MD
BLP 358-006	Marc A. Goldberg, MD

BLP 358-006 David R. Hardten, MD F.A.C.S
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Gregory Henderson, MD
BLP 358-006 John D. Hunkeler, MD
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Bruce H Koffler, MD
BLP 358-006 Subinvestigator:
BLP 358-006 Joseph H. Krug, MD
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Stephen Lane, MD
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Jonathan H. Lass, MD
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
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BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:

BLP 358-006 Carl V. Migliazzo, MD
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Don J. Perez-Ortiz, MD
BLP 358-006 Subinvestigator:
BLP 358-006 David Schwartz, MD
BLP 358-006 O. Dara Stevenson, MD
BLP 358-006 Subinvestigator:
BLP 358-006 Robert H. Stewart, MD, F.A.C.S.
BLP 358-006 William Colby Stewart, MD
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Stephen A. Updegraff, MD, FACS
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 William E. Whitson, MD
BLP 358-006 Micheal Y.Wong, MD
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:
BLP 358-006 Subinvestigator:

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

TO BE COMPLETED BY APPLICANT

The following information concerning [ ] (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study [ ] (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

| any proprietary interest in the product tested in the covered study held by the clinical investigator;

| any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Brian Levy, O.D., M.Sc.	Vice President, Clinical and Medical Affairs
FIRM / ORGANIZATION Bausch & Lomb, Inc.	
SIGNATURE	DATE 8/14/03

Paperwork Reduction Act Statement

1.7 Financial Disclosure Statement (Section 19)

Dr. [redacted] Disclosure information (attachment to Form FDA 3455).

Dr. [redacted] serves as a consultant for Bausch & Lomb. In this capacity, Dr. [redacted] for Bausch & Lomb on surgical techniques, products and services and serves in an advisory role on new product development and programs for the ophthalmic industry.

Dr. [redacted] was a sub-investigator in [redacted] clinical trial consisting of more than [redacted] sites. Dr. [redacted] had multiple sub-investigators. The site contributed [redacted] patients to study [redacted] thus minimizing the potential for the introduction of bias.

Appears This Way
On Original

Deputy Division Director's Summary Review of NDA 50-804

Amended Application

Amendment Submitted:	October 15, 2004
Review Completed:	December 14, 2004
Proposed Tradename:	Zylet
Established Name:	Loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension
Sponsor:	Bausch & Lomb 8500 Hidden River Parkway Tampa, FL 33637 (813) 866-2299 Contact: Julie Townsend
Pharmacologic Category:	Corticosteroid/anti-infective combination
Proposed Indication:	Steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.
Dosage Form and Route of Administration:	Topical ocular ophthalmic suspension

I. Recommendations

A. Recommendation on Approvability

NDA 50-804 (formally listed as NDA 21-675) is recommended for approval. The analytical procedures have been repeated at another laboratory for the steroid portion of the drug product. They are now considered sufficiently validated to establish efficacy for the use of Zylet (loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension) in the treatment of steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

No additional Phase 4 studies are recommended. There are no additional recommended risk management steps for this product.

II. Summary of Clinical Findings

A. Background of Clinical Program

Zylet (loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension) is a topical ocular combination corticosteroid/anti-infective agent. Zylet (LET) is targeted for the treatment of steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. As originally described in the DESI (Drug Efficacy Study Implementation) review for the corticosteroid/anti-infective combinations, these combination products are designed to act as corticosteroids with the anti-infective included to only to minimize the potential increased risk of infection due to corticosteroid use. The corticosteroid component included in Zylet is already approved for steroid responsive diseases as a single agent alone, [Lotemax (loteprednol etabonate ophthalmic suspension 0.5%)]. The anti-infective component included in Zylet is already approved alone as an ophthalmic anti-infective agent [tobramycin ophthalmic solution USP 0.3% (Tobrex)]. The goal of the clinical program was to demonstrate that the addition of tobramycin did not interfere with the efficacy of loteprednolol and that the addition of loteprednolol did not interfere with the ability of tobramycin to kill superficial bacteria thought to be susceptible to tobramycin.

B. Efficacy

The submitted studies in NDA 50-804 attempted to demonstrate equivalence between Zylet and the individual components (loteprednol and tobramycin). The bioequivalence studies were designed to demonstrate the equivalence of Zylet to loteprednolol in providing loteprednolol to the expected site of action (aqueous humor). Protocol 358-005 (Study 5) and 358-006 (Study 6) were pilot and pivotal clinical pharmacology studies, respectively. These studies are subject to review by the Clinical Pharmacology and Biopharmaceutics Division. Study 6 was conducted in male and female patients undergoing routine cataract surgery. Aqueous humor concentrations of loteprednol etabonate at two time points 40- and 60-minutes were compared following topical administration of 4 drops of the test and reference products over a period of 10 minutes. The "bioequivalence" study 358-006 included two sampling points at 40 and 60 minutes for all subjects. The smaller pilot Study 5 used 20 and 40 minutes sampling points. This approach to establishing "bioequivalence" was not consistent with the standard method of pharmacokinetics because it did not use sampling at several time points to determine the rate (Cmax) and extent of absorption (AUC). Since there is no established Cmax or AUC associated with any clinical efficacy parameter, the Clinical Division had no basis to require that equivalence be established for either Cmax or AUC. The trial design itself was accepted by Agency in the early 1990's with the input of members of the Biopharm Group but not current members of the Division of Pharmaceutical Evaluation-III.

As part of the study design, the Clinical Division recommended using a 95% confidence interval approach to establish bioequivalency (as opposed to the 90% confidence interval suggested by OCPB) at both 40- and 60-minutes time points. An 80-125% acceptance interval was also selected, borrowing in effect the two 1-sided t test approach used for bioequivalency testing and adapting it for a clinical endpoint. Because of their concern on the proposed study design, and its possible use by other sponsors as a method of bioequivalency testing, OCPB in consultation with Mr. Don Schuirmann (Office of Biostatistics), the originator of the current FDA bioequivalence approach, made the following recommendation:

"Although the Clinical Division has accepted this BE approach (based on two time points in the aqueous humor) for the approval of Loteprednol Etabonate 0.5%/tobramycin 0.3% ophthalmic combination product, the Office of Clinical Pharmacology and Biopharmaceutics recommends that this approach not be regarded as a precedent for the approval of future combination products for ophthalmic use without the validation of the approach."

The Division of Scientific Investigation HFD-48 conducted inspection of the analytical laboratory [ ] in connection with method validations and discrepancies in study data in the bioequivalence study 358-006. Based on the DSI comments in Form 483, the sponsor performed a re-analysis of the bioequivalence data excluding almost — of the collected data. While the 95% confidence interval at 60-minute time point of the re-analyzed samples was within the range of 80%-125%, that at the 40-minute time point remained outside this range.

The mean aqueous humor concentrations of the test and reference products were 2.8 (range 0 – 32.9, SD ±2.5, N=346) and 2.4 (range 0-21.8, SD ±2.1, N=348) ng/mL at the 40-minute time point. The respective values at the 60-min time point were 4.1 (range 0 – 12.1, SD ±2.2, N=360) and 3.8 (range 0-17.8, SD ±2.3, N=365) ng/mL. The 95% confidence intervals were 77.7-95.5% and 81.5-99.7%, respectively for the 40- and 60-min time points, and the respective point estimates were 1.16 and 1.11. Thus, the product was not within the expected "bioequivalence" at the 40-minute time point although it was higher and within the range for the 60-minute time point.

The potential interference by loteprednolol on the activity of tobramycin evaluated using an in vitro microbial kill rate method since, the anti-infective is included for its local effect against superficial bacterial ocular infection. The negative control group (sterile saline) showed recovery values nearly equivalent to the initial inoculum at all time periods. Each of the active agents, LET and tobramycin demonstrate effective and equivalent kill rates. The majority of the organisms are killed within seconds. For all organisms, the colony count is zero by 30 minutes and remained at zero at 60 minutes for each product.

Based on questions raised from the review of the [ ] facility with the subsequent removal of large amounts of the bioequivalence data from the dataset, the bioequivalence studies submitted in NDA 50-804 are not considered sufficient as presently submitted. Based on the observations identified in the 483 inspection of [ ] there is concern about the validity and integrity of the final dataset used to establish bioequivalency between Zylet and Lotemax. It was recommended that the data be adequately validated at another facility.

A telecon was held on 12/1/04 between Drs. Bashaw and Boyd, and Mr. Raphael Rodriguez of the FDA and Ms. Julie Townsend of Bausch and Lomb. In this telecom Dr. Bashaw informed the sponsor that the statistical analysis contained in the re-submission was inadequate as detailed in the biopharm review, as it attempted to validate the [ ] laboratory data. The FDA emphasized that the [ ] data was not acceptable. But the agency was willing to consider an independent re-analysis of the remaining samples as a standalone assessment of bioavailability. During the telecom the sponsor was asked to repeat the statistical analysis for bioequivalency on just the [ ] database.

Table 1. Loteprednol concentration (ng/mL) by treatment group: ITT analysis population ([ ] dataset)

	40 min Treatment		60 min Treatment	
	Lotemax	LET	Lotemax	LET
N	340	330	339	341
Mean	2.642	2.776	3.722	4.177
SD	2.579	2.541	2.408	2.859
Median	2.045	2.225	3.290	3.680
Min	[ ]			
Max				

Table 2. Loteprednol concentration (ng/mL) by treatment group: ITT analysis population (subset of population analyzed by [ ] with sufficient remaining volume)

	40 min Treatment		60 min Treatment	
	Lotemax	LET	Lotemax	LET
N	58	58	61	44
Mean	2.136	2.561	3.030	3.212
SD	1.481	1.782	1.694	1.732
Median	1.830	1.880	2.510	3.020
Min	[ ]			
Max				

Additionally, the Sponsor has provided a head-to-head comparison of the [ ] and [ ] assays between the 105 samples tested at [ ] where previous results

were also available from [ ] The correlation coefficient of this comparative analysis is 0.8.

	40min Data		60min Data	
	Loteprednol N=58	ZYLET N=58	Loteprednol N=61	ZYLET N=44
Mean +/- STD	2.136+/-1.481	2.561+/-1.782	3.030+/-1.694	3.212+/-1.732
95% Confidence Interval	-0.395 to 0.086 (67.4-108.9%)		-0.322 to 0.189 (72.5-120.8%)	

The analysis provided by the sponsor and summarized in the table above still fails to demonstrate bioequivalence between the two formulations.

The failure to demonstrate bioequivalence here is due to a number of reasons including the number of observations, the nature of the observations (single timepoints), and the route of administration (topical ocular) translating into a very high variability with %CV's on the order of 69%. While the mean data does show about a 0.5ng/mL difference in concentrations between the Loteprednol alone and Zylet groups, the median values are more in-line at the 40min timepoint (1.83 vs. 1.88ng/ml) but different again at the 60min timepoint (3.03 vs. 3.21). The ranges are almost superimposable.

Biopharm Team Leader Recommendation: "Given the demonstrated higher ocular concentrations for Zylet vs. loteprednol alone, it is clear that the Zylet product cannot be less effective than the single entity loteprednol product. The proposed indication for this product is "*For the treatment of steroid-responsive inflammatory ocular conditions for which corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.*" Based on the data, the Office of Clinical Pharmacology and Biopharmaceutics cannot make a finding of bioequivalence between Zylet and the single entity loteprednol drops based on the data provided. While we concede that the product produces levels in the eye that are at least as efficacious as those of the single entity product, we cannot, based on the concentration data, address safety directly. The issue of ocular safety is an issue for the reviewing medical officer, however, given the toxicities of corticosteroids it is highly unlikely that ocular administration of these doses would result in systemic toxicity. Should the medical review team conclude that this product represents no safety issues, we would have no objection to this product being marketed, provided that labeling indicate that intraocular aqueous humor levels taken at 40 and 60 min. after administration were not equivalent to those of the single entity product."

Clinically, this loteprednol is not as potent as other corticosteroids and there is no additional safety concern with the marginally higher level of loteprednol obtained from Zylet.

C. Safety

All of the components included in Zylet are well known and based on studies originally submitted with Lotemax, are considered safe for the proposed indication. The submitted studies in NDA 50-804 do not raise any new concerns and demonstrate an acceptable safety profile with the use of LET for the treatment of steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

D. Other Disciplines

There are no outstanding review issues related to Chemistry, Sterility Assurance or Manufacturing of the drug substance or drug product. There were no new issues identified in the Pharmacology/Toxicology Review and no previously outstanding issues related to Pharmacology/Toxicology.

E. Labeling

Labeling of the drug product has been modeled after the other corticosteroid/anti-infective combination drug products.

F. Other Outstanding Issues

Clarification was obtained regarding the patent certification. The applicant is making a Paragraph II Certification covering the antibiotic portion of the product which is not listed in the Orange Book because it is an antibiotic. The applicant is making a Paragraph IV Certification covering an NDA which they own.

Wiley A. Chambers, MD
Deputy Division Director, DAAODP, HFD-550

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

/s/

Wiley Chambers
12/14/04 04:01:52 PM
MEDICAL OFFICER

Rodriguez, Raphael R

From: Townsend, Julie [Julie_Townsend@bausch.com]
Sent: Monday, December 13, 2004 12:52 PM
To: 'rodriguezr@cder.fda.gov'
Subject: FW: N50-804 - Zylet Labeling


AB35807-9004301 Carton1.pdf (8...


N21675 Label 2_13_041.doc (13..


AB35807-9004301 Carton.pdf (88...

Hi Raphael,

See if you can open this one. I'm calling you now. <<AB35807-9004301 Carton1.pdf>>
Thanks,

Julie

> -----Original Message-----
> From: Townsend, Julie
> Sent: Monday, December 13, 2004 11:19 AM
> To: 'rodriguezr@cder.fda.gov'
> Cc: Handley, Donald
> Subject: N50-804 - Zylet Labeling
>
> Hi Raphael,
>
> Per Dr. Lim's telephone request of 12/10/2004, please find attached a
> corrected pdf file for the 5mL carton containing the statement "Store
> upright at..." (same statement as the other cartons).

A MSWord file of the package insert is also attached. Also per Dr. Lim's request, the tonicity statement has been corrected to be

> consistent with the container cartons. It now reads "mOsmol/kg". No
> other changes have been made.
>
> I will follow this email up with a hard copy submission to the NDA
> today.
>
>
> <<N21675 Label 12_13_041.doc>> <<AB35807-9004301 Carton.pdf>>
>
> Thanks and best regards,
>
> Julie
>
> Julie Townsend, MPH
> Manager, Regulatory Affairs
> Tel: 813.866.2299
> Fax: 813.975.7757
>

Bausch & Lomb
150 Years of Perfecting Vision, Enhancing Life (TM)

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Fax Cover Sheet

Bausch & Lomb

8500 Hidden River Parkway
Tampa, FL 33637
Phone: (813) 866-2299
Facsimile: (813) 975-7757

Deliver To:	Raphael Rodriguez	From:	Julie Townsend, MPH
	RMN320		Manager, Regulatory Affairs
Fax:	301.827.2531		
Phone:	301.827.2090	Date:	December 13, 2004
Re:	NDA 50-804 (21-675) Zylet	CC:	

No. of pages: (including cover sheet) 2

☐ Urgent ☑ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

Hi Raphael,

Per your request, I am faxing the 5 mL carton for Zylet. This is a same carton I emailed this morning. I will submit a hard copy of this fax via overnight mail today.

Thanks and best regards,

Julie

Julie Townsend, MPH
Manager, Regulatory Affairs

CONFIDENTIAL/ Please forward immediately / CONFIDENTIAL

7 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Deputy Division Director's Summary Review of NDA 21-675

Original Application

Submitted:	September 8, 2003
Received:	September 8, 2003
Review completed:	July 6, 2004
Proposed Tradename:	Zylet
Established Name:	Loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension
Sponsor:	Bausch & Lomb 8500 Hidden River Parkway Tampa, FL 33637 (813) 866-2299 Contact: Julie Townsend
Pharmacologic Category:	Corticosteroid/anti-infective combination
Proposed Indication:	Steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.
Dosage Form and Route of Administration:	Topical ocular ophthalmic suspension

I. Recommendations

A. Recommendation on Approvability

NDA 21-675 is not recommended for approval. The analytical procedures provided with the submitted studies in NDA 21-675 for the steroid portion of the drug product are not sufficiently validated to establish efficacy (bioequivalence) for the use of Zylet (loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension) in the treatment of steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

No additional Phase 4 studies are recommended. There are no additional recommended risk management steps for this product.

Deputy Division Director's Summary Review of NDA 21-675

II. Summary of Clinical Findings

A. Background of Clinical Program

Zylet (loteprednol etabonate 0.5%/tobramycin 0.3% ophthalmic suspension) is a topical ocular combination corticosteroid/anti-infective agent. Zylet (LET) is targeted for the treatment of steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. As originally described in the DESI (Drug Efficacy Study Implementation) review for the corticosteroid/anti-infective combinations, these combination products are designed to act as corticosteroids with the anti-infective included to only to minimize the potential increased risk of infection due to corticosteroid use. The corticosteroid component included in Zylet is already approved for steroid responsive diseases as a single agent alone, [Lotemax (loteprednol etabonate ophthalmic suspension 0.5%)]. The anti-infective component included in Zylet is already approved alone as an ophthalmic anti-infective agent [tobramycin ophthalmic solution USP 0.3% (Tobrex)]. The goal of the clinical program was to demonstrate that the addition of tobramycin did not interfere with the efficacy of loteprednolol and that the addition of loteprednolol did not interfere with the ability of tobramycin to kill superficial bacteria thought to be susceptible to tobramycin.

B. Efficacy

The submitted studies in NDA 21-675 attempted to demonstrate equivalence between Zylet and the individual components (loteprednol and tobramycin). The bioequivalence studies were designed to demonstrate the equivalence of Zylet to loteprednolol in providing loteprednolol to the expected site of action (aqueous humor). Protocol 358-005 (Study 5) and 358-006 (Study 6) were pilot and pivotal clinical pharmacology studies, respectively. These studies are subject to review by the Clinical Pharmacology and Biopharmaceutics Division. Study 6 was conducted in male and female patients undergoing routine cataract surgery. Aqueous humor concentrations of loteprednol etabonate at two time points 40- and 60-minutes were compared following topical administration of 4 drops of the test and reference products over a period of 10 minutes. The "bioequivalence" study 358-006 included only two sampling points at 40 and 60 minutes for all subjects. The smaller pilot Study 5 used 20 and 40 minutes sampling points. This approach to establishing "bioequivalence" was not consistent with the standard method of pharmacokinetics because it did not use sampling at several time points to determine the rate (Cmax) and extent of absorption (AUC). Since there is no established Cmax or AUC associated with any clinical efficacy parameter, the Clinical Division had no basis to require that equivalence be established for either Cmax or AUC. The trial design itself was accepted by Agency in the early 1990's with the input of members of the Biopharm Group but not current members of the Division of Pharmaceutical Evaluation-III.

As part of the study design, the Clinical Division recommended using a 95% confidence interval approach to establish bioequivalency (as opposed to the 90% confidence interval suggested by OCPB) at both 40- and 60-minutes time points. An 80-125% acceptance interval was also selected, borrowing in effect the two 1-sided t test approach used for bioequivalency testing and adapting it for a clinical endpoint. Because of their concern on the proposed study design, and its possible use by other sponsors as a method of bioequivalency testing, OCPB in consultation with Mr. Don Schuirmann (Office of Biostatistics), the originator of the current FDA bioequivalence approach, made the following recommendation:

"Although the Clinical Division has accepted this BE approach (based on two time points in the aqueous humor) for the approval of Loteprednol Etabonate 0.5%/tobramycin 0.3% ophthalmic combination product, the Office of Clinical Pharmacology and Biopharmaceutics recommends that this approach not be regarded as a precedent for the approval of future combination products for ophthalmic use without the validation of the approach."

The Division of Scientific Investigation HFD-48 conducted inspection of the analytical laboratory [ ] in connection with method validations and discrepancies in study data in the bioequivalence study 358-006. Based on the DSI comments in Form 483, the sponsor performed a re-analysis of the bioequivalence data excluding almost — of the collected data. While the 95% confidence interval at 60-minute time point of the re-analyzed samples was within the range of 80%-125%, that at the 40-minute time point remained outside this range.

The mean aqueous humor concentrations of the test and reference products were 2.8 (range 0 – 32.9, SD ±2.5, N=346) and 2.4 (range 0-21.8, SD ±2.1, N=348) ng/mL at the 40-minute time point. The respective values at the 60-min time point were 4.1 (range 0 – 12.1, SD ±2.2, N=360) and 3.8 (range 0-17.8, SD ±2.3, N=365) ng/mL. The 95% confidence intervals were 77.7-95.5% and 81.5-99.7%, respectively for the 40- and 60-min time points, and the respective point estimates were 1.16 and 1.11. Thus, the product was not within the expected "bioequivalence" at the 40-minute time point although it was higher and within the range for the 60-minute time point.

The potential interference by loteprednolol on the activity of tobramycin evaluated using an in vitro microbial kill rate method since, the anti-infective is included for its local effect against superficial bacterial ocular infection. The negative control group (sterile saline) showed recovery values nearly equivalent to the initial inoculum at all time periods. Each of the active agents, LET and tobramycin demonstrate effective and equivalent kill rates. The majority of the organisms are killed within seconds. For all organisms, the colony count is zero by 30 minutes and remained at zero at 60 minutes for each product.

Based on questions raised from the review of the [ ] facility with the subsequent removal of large amounts of the bioequivalence data from the dataset, the bioequivalence studies submitted in NDA 21-675 are not considered sufficient as presently submitted. Based on the observations identified in the 483 inspection of [ ], there is concern about the validity and integrity of the final dataset used to establish bioequivalency between Zylet and Lotemax. It is recommended that the data be adequately validated at another facility.

C. Safety

All of the components included in Zylet are well known and based on studies originally submitted with Lotemax, are considered safe for the proposed indication. The submitted studies in NDA 21-675 do not raise any new concerns and demonstrate an acceptable safety profile with the use of LET for the treatment of steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

D. Other Disciplines

There are no outstanding review issues related to Chemistry, Sterility Assurance or Manufacturing of the drug substance or drug product. There were no new issues identified in the Pharmacology/Toxicology Review and no previously outstanding issues related to Pharmacology/Toxicology.

E. Labeling

Discussions on the labeling of the drug product are expected to be modeled after all of the other corticosteroid/anti-infective combination drug products. Specific details will be finalized after the issues of bioequivalence have been resolved.

F. Other Outstanding Issues

Clarification is needed regarding the patent certification. The applicant appears to make a Paragraph II Certification covering an ingredient which is not listed in the Orange Book as having a relevant patent. The applicant appears to make a Paragraph IV Certification covering an NDA which they own. Clarification of these patent certifications should be submitted.

Wiley A. Chambers, MD
Deputy Division Director, DAAODP, HFD-550

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

/s/

Wiley Chambers
7/6/04 04:10:43 PM
MEDICAL OFFICER

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✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

9/8/03

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
Bausch & Lomb, Inc.
8500 Hidden River Parkway
Tampa, FL 33637

2. TELEPHONE NUMBER *(Include Area Code)*
(813) 866.2299

3. PRODUCT NAME
Zylet (TM) (loteprednol etabonate and tobramycin ophthalmic suspension), 0.5% / 0.3%

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
N021675

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4574

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Julie Townsend	Associate Manager, Regulatory Affairs	9/8/03

FORM FDA 3397 (1/03)

PSC Media Arts (301) 443-6090

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

12/13/04

NDA 50-804

Bausch & Lomb, Inc.
Attention: Julie Townsend, MPH
Manager, Regulatory Affairs
8500 Hidden River Parkway
Tampa, FL 33637

Dear Ms. Townsend:

Please refer to your New Drug Application (NDA) submitted September 8, 2003, under the Federal Food, Drug, and Cosmetic Act for Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) 0.5%/0.3%. We also acknowledge receipt on October 15, 2004, of your October 14, 2004, Class-1 resubmission.

We refer to the guidance document issued by the Agency in May 1998, *Guidance for Industry and Reviewers Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act*. This guidance document defines the administrative actions required by the Agency for reviewing and approving antibiotic drug applications that were submitted after November 21, 1997. We also refer to the *Federal Register* notice Docket Number: 99N-3088, *Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs* issued January 24, 2000, which lists the active drug substances, including any derivative thereof, that are directly affected by the repeal of Section 507.

The combination product, loteprednol etabonate and tobramycin ophthalmic suspension is considered to be an antibiotic. The Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) 0.5%/0.3% application that was previously numbered as NDA 21-675 has been re-numbered to NDA 50-804. All documentation regarding this application should be directed to NDA 50-804 from this date forward.

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}
Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Wiley Chambers
12/13/04 02:15:34 PM

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

December 13, 2004

BAUSCH & LOMB

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA 50-804
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3% (Zylet™)
Hard Copy of Email from 12/13/04 - Revised 5mL Carton and Package Insert

Dear Dr. Chambers:

The purpose of this submission is to provide a hard copy of the email sent to the Agency on 12/13/04 containing the revised 5mL carton and package insert with the Division's recommended changes.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this application, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Sincerely,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

Attachments

8500 Hidden River Parkway Tel 813 975 7760
Tampa FL 33637
www.bausch.com

December 10, 2004

BAUSCH & LOMB

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA 50-804 (formerly 21-675)
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3%
(Zylet™)
Hard Copy of Email from 12/10/04 - Revised Carton and Container Labels

Dear Dr. Chambers:

The purpose of this submission is to provide a hard copy of the email sent to the Agency on 12/10/04 containing the revised carton and container labels with the Division's recommended changes.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this application, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Sincerely,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

Attachments

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

December 9, 2004

BAUSCH & LOMB

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: **NDA 50-804 (formerly 21-675)**
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3%
(Zylet™)
Hard Copy Facsimile of Initialed & Dated, Final Agreed Upon Package Insert
(12/9/04)

Dear Dr. Chambers:

The purpose of this submission is to provide a hard copy of the final agreed upon label (initialed and dated), which was faxed to the Agency on 9 December 2004.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this application, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Sincerely,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

Attachments

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

December 8, 2004

2000(c)

NEW CORRESP

BAUSCH & LOMB

RECEIVED
DEC 0 9 2004
MEGA/CDER

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3%
(Zylet™)
Hard Copies of Email Correspondence from 12/8/2004

Dear Dr. Chambers:

The purpose of this submission is to provide hard copies of information sent via email on 8 December 2004. The first email included the revised Package Insert as agreed upon via teleconference with the Agency on 7 December 2004. The second email was in response to information requested by Dr. Lim regarding superficial punctate keratitis incidence in study BLP 358-003. The emails and their attachments are included.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this application, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Sincerely,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

Attachments

DUPLICATE

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

December 7, 2004

DUPLICATE

BAUSCH & LOMB

RECEIVED
DEC 0 8 2004
MEGA/CDER

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3%
(Zylet™)
Request for Deferral for Pediatric Study

N-000(PL)
ORIG AMENDMENT

Dear Dr. Chambers:

The purpose of this submission is to request a deferral of the requirement for pediatric studies *until after the NDA approval per 21 CFR 314.55.* B&L commits to performing a pediatric study in a minimum of 60 patients 0 – 6 years of age. The projected date for completion of the study will be within 24 months of the NDA's approval.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this application, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Sincerely,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

Attachments

500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

ORIGINAL

December 2, 2004

BAUSCH & LOMB

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DEC 0 3 2004
MEGA/CDER

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

N-000(83)
ORIG AMENDMENT

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3% (Zylet™)
Response to Biopharm Reviewer's Information Request on 12/1/2004

Dear Dr. Chambers:

The purpose of this submission is to provide a copy of information requested via telephone by Biopharmaceutics Team Leader on 1 December 2004. See attached facsimile.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this application, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Sincerely,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

Attachments

DEPARTMENT OF HEALTH & HUMAN SERVICES

NOV 3 2004

Food and Drug Administration
Rockville MD 20857

Julie Townsend, M.PH.
Associate Manager, Regulatory Affairs
Bausch & Lomb, Inc.
8500 Hidden River Parkway
Tampa, Florida 33637

RE: Partial Refund Request for Zylet, NDA 21-675

Dear Ms. Townsend:

This responds to your letter of January 20, 2004, to Dr. Wiley Chambers, Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products (DAAODP),[1] regarding new drug application (NDA) 21-675, Zylet (loteprednol etabonate and tobramycin) Ophthalmic Suspension. You request a review of the amount of the fee paid under the prescription drug user fee provisions of the Federal Food, Drug, and Cosmetic Act (the Act)[2] for Zylet. We have reviewed the pertinent information and have determined Bausch & Lomb (B&L) should have paid a half application fee of $266,700, rather than the full fee of $533,400, for the review of the application for Zylet.[3] Therefore, B&L is eligible for a refund of $266,700.

I. B&L's Request

Referencing a September 10, 2003, phone conversation you had with Dr. Chambers, you state that Dr. Chambers indicated that your Zylet NDA may be considered an original application without clinical data because it is based on a bioequivalence study. Therefore, you believe that B&L may be eligible for a refund of half the fee paid. In subsequent telephone conversations with Raphael Rodriguez, a project manager in the DAAODP, it was recommended that B&L submit a formal request for a review of the user fee amount paid for your Zylet NDA.

II. Background Information for NDA 21-675, Zylet

On September 8, 2003, DAAODP received NDA 21-675 for Zylet for the treatment of steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. The five clinical studies that were included in your submission are briefly described as follows:

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[1] Future refund requests or fee assessment questions should be directed to my attention.
[2] Sections 735 and 736 of the Act (21 U.S.C. 379g and 379h).
[3] FDA was notified that B&L paid $533,400 for NDA 21-675, User Fee ID # 4574 on July 18, 2003

1. 358-002: A randomized, double-masked, placebo-controlled safety and tolerance evaluation of loteprednol etabonate and tobramycin (LET) ophthalmic suspension. The objective of the study was to evaluate the safety and tolerance of LET compared to placebo administered four times daily for 14 days in healthy volunteers.
2. 358-003: A randomized, double-masked, placebo-controlled, parallel group safety evaluation of LET ophthalmic suspension. The objective of this study was to assess the safety of LET administered four times daily for 6 weeks in healthy volunteers.
3. 358-004: A randomized, double-masked, placebo-controlled comparison of the clinical bioequivalence of B&L's LET compared to Lotemax in volunteers exposed to allergen challenge. The objective of this study was to evaluate the clinical bioequivalence of the loteprednol etabonate component of LET to Lotemax in reducing the signs and symptoms associated with acute allergic conjunctivitis induced by a topical allergen challenge.
4. 358-005: A pilot, randomized, single-center comparison of the aqueous humor concentration of loteprednol etabonate following administration of B&L's LET or Lotemax during routine cataract surgery. The objective of this study was to evaluate the bioavailability of LET compared to Lotemax in an ocular penetration model in subjects undergoing cataract surgery.
5. 358-006: A randomized, double-masked, multi-center comparison of the aqueous humor concentration of loteprednol etabonate following administration of B&L's LET or Lotemax during routine cataract surgery. The objective of this study was to evaluate the bioavailability of B&L's LET compared to Lotemax in an ocular penetration model in patients undergoing cataract surgery using local anesthetic in one eye.

III. Criteria for Assessment of Application Fees

Under section 736(a)(1)(A)(i) of the Act, a full application fee is required for "a human drug application for which clinical data (other than bioavailability or bioequivalence studies) with respect to safety or effectiveness are required for approval." Under section 736(a)(1)(A)(ii) of the Act, half of a full application fee is required for "a human drug application for which clinical data with respect to safety or effectiveness are not required."

IV. Evaluation of B&L's Request: Studies Required for Approval

We have contacted DAAODP, and they stated that even though you submitted both safety and bioequivalence studies, the safety studies were not required for approval. They further stated that your application is potentially approvable based only on the bioequivalence studies, once they are sufficiently validated.[4] Because clinical data (other than bioavailability or bioequivalence studies) are not required for approval, B&L should have submitted a half fee of $266,700. Consequently, your refund request is granted.

[4] DAAODP's July 7, 2004, letter conveys the conditions that need B&L's satisfactory response before the application may be approved.

According to FDA records, FDA was notified of B&L's payment of $533,400 for NDA 21-675 on July 18, 2003. Therefore, we have asked the Office of Financial Management (OFM) to refund B&L one-half of the application fee paid, $266,700. You should receive a refund of $266,700. If you do not receive a refund within 30 days of this letter, please contact Pothen (Sunny) Joseph (OFM) at 301-827-5086.

If you have further questions regarding this matter or other user fee questions, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

8500 Hidden River Parkway Tel 813 975 7700
Tampa FL 33637
www.bausch.com

N-000

November 1, 2004

BAUSCH & LOMB

ORIG AMENDM

RECEIVED

NOV 0 2 2004

MEGA / CDER

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products (HFD-550)
Center for Drug Evaluation and Research
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3%
(Zylet™)
Response to Biopharm Reviewer's Comments of 10/22/2004

Dear Dr. Chambers:

The purpose of this submission is to provide responses to email comments received 22 October 2004 from the Biopharmaceutics Reviewer and telephone comments from the Biopharmaceutics Team Leader on 26 October 2004.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this application, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Sincerely,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

Attachments

ORIGINAL

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
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October 14, 2004

BAUSCH & LOMB

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and
Ophthalmic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
U.S. Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3% (Zylet™)
Type 1 Resubmission – Complete Response

Dear Dr. Chambers:

B&L considers this amendment a complete response to the 07 July 2004 Approvable letter, which cited the following deficiencies:

1. Review of the analytical portion of the BLP 358-006 dataset has called into question the integrity and validity of the dataset. The methods and procedures used to correct the deficiencies cited in the inspection report should be submitted. A corrected dataset should be submitted. Any additional analyses of the analytic procedures conducted at the original facility or any alternative facilities should be submitted.
2. Clarification is needed regarding the patent certification. The application includes a Paragraph II certification covering an ingredient which is not listing the "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book) as having a listed patent. The application also includes a Paragraph IV Certification covering an NDA which you appear to own. Clarification of these patent certifications should be submitted.

Additionally, the requested safety update per 21 CFR 314.50(d)(5)(vi)(b) is included within this submission.

Bausch & Lomb believes that this complete response meets the criteria of a Type 1 resubmission and hereby requests this designation.

We acknowledge that the agency will continue to work with us on the product labeling, and look forward to receiving any comments from the Division on the labeling soon. Likewise, we acknowledge your request to submit three copies of the introductory promotional materials to DDMAC. These materials will be submitted when they become available. We additionally request to receive official notification on the acceptability of the proposed tradename, Zylet.

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September 10, 2004

BAUSCH & LOMB

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and
Ophthalmic Drug Products (HFD-550)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
U.S. Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3% (Zylet™)
Proposal for Complete Response to Action Letter Item #1

Dear Dr. Chambers:

The purpose of this submission is to provide to the agency Bausch & Lomb's proposal for response to the first item listed on the approvable letter dated 7 July 2004. The activities outlined in this proposal have been thoroughly discussed and agreed upon with Dr. Dennis Bashaw, Team Leader Division of Pharmaceutical Evaluation III. We anticipate completing the activities and submitting the complete response by mid-October and therefore request receiving any comments from the Agency on the proposal by 8 October 2004.

Additionally, meeting minutes from the 11 August 2004 teleconference between Bausch & Lomb and agency representatives are provided, along with a post-meeting note on a telephone contact between Dr. Bashaw and Don Handley, Director, Regulatory Affairs, B&L, on 12 August 2004.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this amendment, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Best regards,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

Bausch & Lomb looks forward to working with the Division to complete the review and approval of this application as expeditiously as possible. If you have any questions regarding this amendment, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Best regards,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

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Tel 813 975 7700
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June 15, 2004

ORIGINAL

BAUSCH & LOMB

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research (HFD-550)
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

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JUN 16 2004
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N-000(Bm)
ORIG AMENDMENT

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3% (Zylet™)
Clinical: Amendment to a Pending Application
Response to Information Request Email of 05/26/04

Dear Dr. Chambers:

The purpose of this submission is to provide responses to Raphael Rodriguez' email information request of May 26, 2004.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this amendment, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Best regards,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

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BAUSCH & LOMB

June 14, 2004

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research (HFD-550)
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3% (Zylet™)
Amendment to a Pending Application
Clinical Study BLP 358-006

Dear Dr. Chambers:

The purpose of this submission is to provide follow-up information with regard to the corrective action plan for the contract analytical laboratory [ ], as well as the subsequent re-analysis of the bioequivalence data for study BLP 358-006. A summary of the completed action plan activities is included.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this amendment, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Best regards,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

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June 7, 2004

BAUSCH & LOMB

N-000(BL)

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research (HFD-550)
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RECEIVED
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ORIG AMENDMENT

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3%
(Zylet™)
Amendment to a Pending Application

Dear Dr. Chambers:

The purpose of this submission is to provide a Pediatric Assessment and revised draft package insert labeling which includes a statement for the pediatric use of Zylet in [ ]. This assessment is based on the provisions outlined in the Pediatric Research Equity Act of 2003. Pediatric requirements were not addressed in the original NDA, dated 8 September 2003, prior to this law's enactment.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this amendment, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Best regards,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

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BAUSCH & LOMB

May 19, 2004

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research (HFD-550)
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3% (Zylet™)
Clinical: Amendment to a Pending Application
Response to Information Request Email of 05/17/04

Dear Dr. Chambers:

The purpose of this submission is to provide responses to Dr. Lucious Lim's email information request of May 13, 2004, received from Raphael Rodriguez on May 17, 2004.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this amendment, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Best regards,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

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BAUSCH & LOMB

May 10, 2004

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research (HFD-550)
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3% (Zylet™)
Amendment to a Pending Application

Dear Dr. Chambers:

The purpose of this amendment is to provide the information requested by Dr. Su Tso (Chemistry Reviewer) regarding the method validation package for NDA 21-675. The following requested information is included in this submission:

- Drug substance specifications (tobramycin and sterile loteprednol etabonate)
- Drug product formulation
- Drug product specification
- Revised HPLC methods [redacted] including detailed analytical procedures and validation data
- Material Safety Data Sheets (MSDS) for drug substances
- Tabular Listing of Samples

In accordance with 21 CFR 314.50(d)(1)(v), we certify that a true copy of the information contained in this amendment has been forwarded to the FDA's Orlando District Office. The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this amendment, please contact me at:

Phone (813) 866-2033
Fax (813) 975-7757
E-mail marcus_juliano@bausch.com

Best regards,

Marcus Juliano
Regulatory Affairs Specialist

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 50-804	Efficacy Supplement Type SE-	Supplement Number	
Drug: Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) 0.5%/0.3%		Applicant: Bausch & Lomb, Inc.	
RPM: Raphael R. Rodriguez		HFD- 550	Phone # (301) 827-2519

Application Type: ( ) 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review, if completed for this application. If not completed, or you otherwise have questions about whether an application is a 505(b)(1) or 505(b)(2) NDA, see Appendix A.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information that is no longer correct.** ( ) Confirmed and/or corrected	Reference Listed Drug (NDA #, Drug name): NDA 20-583 Lotemax (loteprednol etabonate ophthalmic suspension) 0.5% NDA 20-803 Alrex (loteprednol etabonate ophthalmic suspension) 0.2% NDA 50-541 Tobrex (tobramycin ophthalmic solution, USP) 0.3% ANDA 64-052 Tobramycin Ophthalmic Solution, USP, 0.3%

Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	New Combination
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	12/15/2004
❖ Special programs (indicate all that apply)	( ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 4574
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation (X) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions)

	(X) Other (specify) Paid in FULL. Submitted bioequivalence study. 11/3/2004 Partial refund was granted.
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) I (X) II ( ) III (X) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be granted effective approval (but may be tentatively approved if it is otherwise ready for approval) until the date that the patent to which the certification pertains expires.	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity))*	( ) N/A (no paragraph IV certification) (X) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other*	(X) Yes ( ) No (X) Yes ( ) No

paragraph IV certifications, skip to next box below (Exclusivity).

*If "**No**," continue with question (3).*

( ) Yes ( ) No

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). The patent owner (or its representative) may, but is not required, to provide such notification (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

( ) Yes ~~(X)~~ No

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to next box below (Exclusivity).*

*If "**No**," continue with question (5).*

( ) Yes ~~(X)~~ No

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). (The patent owner (or its representative) may, but is not required, to provide such notification (see 21 CFR 314.107(f)(2))). Note that the applicant has until the **later** of the following dates to provide the Division with this written notice: (a) the date marking the end of the 45-day period described in question (1), above, or (b) the date that the Division completes its review of the application (see 21 CFR 314.107(f)(2))).

*If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to next box below (Exclusivity).*

*If "**Yes**," a stay of approval may be in effect, answer the following questions.*

( ) Yes ( ) No

(6) (a) Was the patent subject to the paragraph IV certification submitted to FDA on or after August 18, 2003?

(Note: This can be determined by checking with **[the Orange Book staff?]**.)

*If "**No**," skip to question 7. If "**Yes**," continue with part (b).*

(b) Was the patent also submitted to FDA before the date that this 505(b)(2) application was submitted as substantially complete?

~~(X)~~ Yes ( ) No

*If "**No**," there is no stay of approval based on the paragraph IV certification for this patent. If "**Yes**," continue with question (7).*

(7) (a) Have 30 months (or an alternate length of time ordered by the court, if any) passed from the date the patent owner received the applicant's notice of certification for the patent?

(Note: In general, approval of a 505(b)(2) application cannot be made effective (although the application can be tentatively approved) for 30 months from the date that the patent owner receives the applicant's notice of certification if a patent infringement suit is timely initiated as described in question (5) above. However, the court may order that the 30-month period be shortened or lengthened under certain circumstances. If the court has ordered that the 30-month period be altered in a particular case, the applicant is required to submit a copy of the court order to the Division within 10 working days (see 21 CFR 314.107(e))).

~~(X)~~ Yes ( ) No

*If "**No**," go to question (8). If "**Yes**," continue with part (b) of this question.*

(b) Before the expiration of the 30-month (or other) period described in part (a), above, did the district court hearing the patent infringement action decide whether the patent subject to the certification is invalid, unenforceable, or not infringed? (For purposes of this question, a district court decision would include a statement regarding the patent's invalidity, unenforceability, or noninfringement that is part of a settlement order or consent decree entered by the court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement.)

(Note: To answer this question, you should check whether the Division has received a copy of a court order or judgment. The applicant is required to submit a copy of any such document to the Division within 10 working days (see 21 CFR 314.107(e))).

( ) Yes ~~(X)~~ No

*If "**No**," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "**Yes**," continue with part (c) of this question*

(c) Did the district court decide that the patent was invalid, unenforceable, or not infringed?

( ) Yes ( ) No

*If "**Yes**," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "**No**," (i.e., the district court decided that the patent was valid, enforceable, and infringed), continue with part (d) of this question.*

( ) Yes **(X)** No or N/A

(d) If the district court's decision was appealed, has the appellate court issued a decision finding the patent invalid, unenforceable, or not infringed (including a statement to this effect that is part of a settlement order or consent decree entered by the appellate court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement)?

(Note: As mentioned above, the applicant is required to submit a copy of all court orders or judgments to the Division within 10 working days (see 21 CFR 314.107(e)); therefore, you can check to see whether a copy of an appellate court's order or judgment has been submitted.)

*If "**Yes**," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, go to the next box below (Exclusivity).*

*If "**N/A**" (i.e., the district court decision was not appealed) or "**No**" (i.e., the appellate court has not yet issued a decision, or has decided that the patent was infringed), the application cannot be effectively approved until the date the patent expires. (If, before the date the patent expires, the appellate court decides that the patent is invalid, unenforceable, or not infringed, the application may be effectively approved as of the date of the appellate decision, if it otherwise qualifies for effective approval.) Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

( ) Yes **(X)** No

(8) (a) Has the district court hearing the patent infringement action decided whether the patent subject to the certification is invalid, unenforceable, or not infringed? (For purposes of this question, a district court decision would include a statement regarding the patent's invalidity, unenforceability, or noninfringement that is part of a settlement order or consent decree entered by the court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement.)

(Note: To answer this question, you should check whether the Division has received a copy of a court order or judgment. The applicant is required to submit a copy of any such document to the Division within 10 working days (see 21 CFR 314.107(e))).

*If "**No**," a stay of approval is currently in effect until the expiration of the time period described in (7)(a), above. The stay may be terminated or altered if the district court issues a decision regarding the patent's validity, enforceability, or infringement before the expiration of the time period described in (7)(a). If such a decision is issued before this time period expires, answer question (b) below.*

*If "**Yes**," continue with part (b) of this question.*

( ) Yes **(X)** No

(b) Did the district court decide that the patent was invalid, unenforceable, or not infringed?

*If "**Yes**," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in*

this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity). *If "**No,**" (i.e., the district court decided that the patent was valid, enforceable, and infringed), continue with part (c) of this question.* (c) If the district court's decision was appealed, has the appellate court issued a decision finding the patent invalid, unenforceable, or not infringed (including a statement to this effect that is part of a settlement order or consent decree entered by the appellate court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement)? (Note: As mentioned above, the applicant is required to submit a copy of all court orders or judgments to the Division within 10 working days (see 21 CFR 314.107(e)); therefore, you can check to see whether a copy of an appellate court's order or judgment has been submitted.) *If "**Yes,**" there is no stay of approval based on the paragraph IV certification for this patent.* *If "**N/A**" (i.e., the district court decision was not appealed) or "**No**" (i.e., the appellate court has not yet issued a decision, or has decided that the patent was infringed), the application cannot be effectively approved until the date the patent expires. (If, before the date the patent expires, the appellate court decides that the patent is invalid, unenforceable, or not infringed, the application may be effectively approved as of the date of the appellate decision, if it otherwise qualifies for effective approval.) Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, go to the next box below (Exclusivity).*	( ) Yes ~~(X)~~ No or N/A
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3 year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	N/A
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE – 7/7/2004
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes **(X)** Not applicable

• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	6/4/2004; 12/9/2004
• Most recent applicant-proposed labeling	12/13/2004
• Original applicant-proposed labeling	9/8/2003
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	1/29/2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	6/4/2004; 12/9/2004
• Applicant proposed	9/8/2003
• Reviews	6/4/2004; 12/9 & 12/13/2004
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Pediatric studies for ages 0-6 years until 3/31/2007
• Documentation of discussions and/or agreements relating to post-marketing commitments	Listed on the AP letter
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
Memoranda and Telecons	
Minutes of Meetings	
• EOP2 meeting (indicate date)	none
• Pre-NDA meeting (indicate date)	none
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	7/6/2004
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	6/4/2004; 12/13/2004
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	7/1/2004
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	ages 0-6 years in 60 patient
Demographic Worksheet *(NME approvals only)*	N/A
Statistical review(s) *(indicate date for each review)*	N/A

❖ Biopharmaceutical review(s) *(indicate date for each review)*	6/15/2004; 12/7/2004
Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	4/19/2004
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	4/29/2004; 5/17/2004; 11/29/2004
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	4/29/2004
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	11/7/2003
❖ Facilities inspection (provide EER report)	Date completed: **(X)** Acceptable 2/27/2004 ( ) Withhold recommendation
❖ Methods validation	( ) Completed **(X)** Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	12/19/2003
Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

BAUSCH & LOMB

April 21, 2004

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research (HFD-550)
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3%
(Zylet™)
Amendment to a Pending Application

Dear Dr. Chambers:

The purpose of this submission is to amend the above-mentioned application to include information provided to you via email on 20 April 2004 regarding the Pre-Approval Inspection of the contract analytical laboratory, [redacted].

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this amendment, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Best regards,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

BAUSCH & LOMB

April 19, 2004

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research (HFD-550)
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3%
(Zylet™)
Clinical: Amendment to a Pending Application
Response to Information Request Email of 03/31/04

N-000 (BM)
ORIG AMENDMENT

Dear Dr. Chambers:

The purpose of this submission is to provide a response to Raphael Rodriguez' email request of March 31, 2004. For ease of review, a copy of the email is contained within this response.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this amendment, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Best regards,

Julie Townsend

Julie Townsend, MPH
Manager, Regulatory Affairs

ORIGINAL

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Tampa FL 33637
Tel 813 975 7700
www.bausch.com

BAUSCH & LOMB

April 13, 2004

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research (HFD-550)
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

N-000(BC)

RECEIVED
APR 15 2004
MEGA/CDER

ORIG AMENDMENT

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3% (Zylet™)
CMC: Amendment to a Pending Application
Response to Information Request Fax of 3/24/04

Dear Dr. Chambers:

The purpose of this submission is to provide responses to Dr. Su Tso's fax request of March 24, 2004. For ease of review, the requests from Dr. Tso's faxes are duplicated verbatim in bold font, followed by B&L's response. In addition to the fax request from 3/24/04, we are also including a response to several commitments made in previous CMC amendments.

In accordance with 21 CFR 314.50(d)(1)(v), we certify that a true copy of the information contained in this amendment has been forwarded to the FDA's Orlando District Office. The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this amendment, please contact me at:

Phone (813) 866-2033
Fax (813) 975-7757
E-mail marcus_juliano@bausch.com

Sincerely,

Marcus Juliano
Regulatory Affairs Specialist

ORIGINAL

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

ORIG AMENDMENT N-000-BC

BAUSCH & LOMB

March 2, 2004

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research (HFD-550)
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

ORIGINAL

RECEIVED
MAR 0 4 2004
MEGA/CDER

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3%
(Zylet™)
CMC: Amendment to a Pending Application
Response to Information Request Faxes of 2/2/04 and 2/20/04

Dear Dr. Chambers:

The purpose of this submission is to provide responses to Dr. Su Tso's fax requests of February 2, 2004 and February 20, 2004. For ease of review, the requests from Dr. Tso's faxes are duplicated verbatim in bold font, followed by B&L's response.

In accordance with 21 CFR 314.50(d)(1)(v), we certify that a true copy of the information contained in this amendment has been forwarded to the FDA's Orlando District Office. The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this amendment, please contact me at:

Phone	(813) 866-2033
Fax	(813) 975-7757
E-mail	marcus_juliano@bausch.com

Sincerely,

Marcus Juliano
Regulatory Affairs Specialist

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

November 26, 2003

BAUSCH & LOMB

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3% (Zylet™)
***CMC:* Amendment to a Pending Application**
Response to Information Request Fax of 11/5/03
Revised Post-Approval Stability Protocol

Dear Dr. Chambers:

The purpose of this submission is to provide responses to Dr. Su Tso's fax request of November 5, 2003. For ease of review, the requests from Dr. Tso's fax are duplicated verbatim in bold font, followed by B&L's response.

Additionally, a revised Post-Approval Stability Protocol is included to provide an optional testing [ ] to support an extension of the drug product expiry period.

In accordance with 21 CFR 314.50(d)(1)(v), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office. The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this application, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Sincerely,

Julie Townsend

Julie Townsend, MPH
Associate Manager, Regulatory Affairs

Attachments

8500 Hidden River Parkway
Tampa FL 33637
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November 17, 2003

BAUSCH & LOMB

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension
0.5%/0.3% (Zylet™)
Pharmacology / Toxicology: Amendment to a Pending Application

Dear Dr. Chambers:

Reference is made to the request for information from Asoke Mukherjee (NonClinical Pharmacology and Toxicology reviewer) as forwarded in an email message from Raphael Rodriguez on November 6, 2003. Our response to the request as related to Study 0460LP27.001 *6 Month Ocular Toxicity Study in Dutch Belted Rabbits (19 February 1999)* is provided in this submission.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this application, please contact me at:

Phone (813) 866-2299
Fax (813) 975-7757
E-mail julie_townsend@bausch.com

Sincerely,

Julie Townsend

Julie Townsend, MPH
Associate Manager, Regulatory Affairs

Attachments

To: Julie Townsend, MPH
Associate Manager, Regulatory Affairs
Bausch & Lomb
Phone: 813-866-2299 Fax: 813-975-7757

From: Su C. Tso, Ph. D.
Review chemist, HFD550
(301) 827-2539 phone
(301) 827-2531 fax
e-mail: Tsos@cder.fda.gov.

Date: Nov. 5, 2003

Application #: NDA 21-675

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

Drug substance:

1. Upon receipt of the drug substances from the suppliers, what tests and acceptance criteria will be performed at Bausch & Lomb facility to insure identity and quality?

2. CMC information for the NDA application is referenced to ANDA 64-052. The analytical methods for assay and impurity proposed in the NDA application is method [ ] (pg. 010, vol. 1.02), whereas the methods used in ANDA 64-052 is [ ] Please explain the differences.

3. Please add [ ] to the drug substance loteprednol etabonate specification.

4. The HPLC method is described on pg. 062. vol. 1.01 as [ ] however the validation on pg. 174, vol. 1.01 refers to the method as [ ] Is this the same method with a method # change. If so, is this method the currently approved assay and impurity method for loteprednol etabonate in NDA 20-583 and NDA 20-803 (provide the supplement # and the date of approval if applicable)?

5. The analytical procedure for assay and impurity of tobramycin is listed as [ ] on pg. 66, but for the validation, it refers to as [ ] on pg. 157? Has this method be submitted to ANDA 64-052 for approval? If so, provide the supplement # and the approval date. In addition, NDA 64-052, the analytical procedure for assay and impurity is designated as [ ] but in the current application, you use [ ] Please clarify the differences.

Drug product:

1. What will be the production lot size for the drug product?

2. Drug product specifications on Pg. 127, vol. 1.05, and pg. 005 vol. 1.10 are different. Please provide these specifications (release and stability) in a single Table form for ease of review.

3. Where are the [ ] data located in the NDA?

4. Provide Information on [ ] printing ink, and label colorant for the label. If the information is contained in DMFs, please provide the DMF # and letters of authorization (specify the document submission dates and page number pertaining to the supporting information) to the DMFs.

5. On pg. 126, vol. 1.07, the marketed product and the primary stability batches are labeled with different label adhesive. Is there any stability data to demonstrate the compatibility of the label (include adhesive, label colorant, and printing ink) with the drug product in the marketed container/closure system?

   Since the label adhesive used for the marketed product will be different from the label adhesive used for the primary stability batches, please submit extractable/leachable data to demonstrate the compatibility (no impurity from the new label adhesive will be leached into the formulation) of the new label adhesive with the drug product.

6. Are primary stability batches made with [ ]

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

/s/

Su Tso
11/5/03 08:41:46 AM
CHEMIST

telecom by fax

Linda Ng
11/6/03 12:43:58 PM
CHEMIST
No action needed by PM.

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ORIGINAL

October 24, 2003

BAUSCH & LOMB

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

N-000(21)
ORIG AMENDMENT

RECEIVED
OCT 27 2003
MEGA/CDER

RE: **NDA 21-675**
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3%
(Zylet™)
CMC: Amendment to a Pending Applicaton

Dear Dr. Chambers:

Per Paul Stinavage's (Microbiology reviewer) request on October 24, 2003, attached is additional information related to the media fill final reports previously submitted on 7/21/03 in Volume 1.08. These final reports are listed below:

- ❑
- ❑

Attachments for both reports were not included in the original submission. The following are provided herein for each final report.

- ❑ Attachment 1:
- ❑ Attachment 2:
- ❑ Attachment 3:

In accordance with 21 CFR 314.50(d)(1)(v), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office. The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this application, please contact me at:

Phone	(813) 866-2299
Fax	(813) 975-7757
E-mail	julie_townsend@bausch.com

Sincerely,

Julie Townsend

Julie Townsend, MPH
Associate Manager, Regulatory Affairs

Attachments

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

10/30/03

NDA 21-675

Bausch & Lomb
Attention: Julie Townsend, MPH
Associate Manager, Regulatory Affairs
8500 Hidden River Parkway
Tampa, FL 33637

Dear Ms. Townsend:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) 0.5%/0.3%

Review Priority Classification: Standard

Date of Application: September 8, 2003

Date of Receipt: September 8, 2003

Our Reference Number: NDA 21-675

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 7, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the goal date will be July 8, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Attention: Document Room N115
9201 Corporate Blvd
Rockville, MD 20850

If you have any questions, call Raphael R. Rodriguez, MS, Regulatory Project Manager, at (301) 827-2090

Sincerely,

/S/

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief Project Manager
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drugs, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Raphael Rodriguez
10/30/03 09:18:20 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NO FILING ISSUES IDENTIFIED

10/16/03

NDA 21-675

Bausch & Lomb
Attention: Julie Townsend, MPH
Associate Manager, Regulatory Affairs
8500 Hidden River Parkway
Tampa, FL 33637

Dear Ms. Townsend:

Please refer to your September 8, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) 0.5%/0.3%.

We have completed our filing review of your application. At this time, we have not identified any potential review issues. Our filing review is only a preliminary review and deficiencies may be identified during substantive review of your application.

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

/S/

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Carmen DeBellas
10/16/03 04:58:12 PM

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

N-000(B1)

September 26, 2003

ORIG AMENDMENT

BAUSCH & LOMB

Wiley Chambers, MD, Deputy Director
Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products
Center for Drug Evaluation and Research (HFD-550)
Food & Drug Administration
ATTENTION: DOCUMENT CONTROL ROOM
9201 Corporate Blvd
Rockville, MD 20850

RECEIVED
SEP 2 9 2003
MEGA/CDER

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3% (Zylet)
Amendment to Clinical Microbiology Section

Dear Dr. Chambers:

Bausch & Lomb hereby submits an amendment to the original Clinical Microbiology section of the new drug application for loteprednol etabonate and tobramycin ophthalmic suspension, 0.5% / 0.3% (Zylet™). The original Clinical Microbiology section was presubmitted on July 21, 2003 along with the Chemistry, Manufacturing and Controls and Nonclinical Pharmacology and Toxicology sections of the NDA.

The final report for the *in-vitro* microbial kill rate study for the comparison of loteprednol etabonate and tobramycin ophthalmic suspension, 0.5%/03% versus tobramcyin ophthalmic solution, USP, 0.3% was included in the presubmitted Clinical Microbiology section and also in Section 6 (Human Pharmacokinetics and Bioequivalence/Bioavailability) which was submitted with the remainder of the NDA on September 8, 2003. During the review of Section 6 prior to its submission, it was discovered that the final report was missing a page (page 2 of 5 - Attachment A of Final Report) and the attachments were not organized in a manner consistent with the final report.

This amended section includes a complete and organized final report as compared to the copy of the report in the Clinical Microbiology section submitted on July 21, 2003. The copy of the final report in Section 6 was organized correctly in the September 8, 2003 submission.

If you have any questions regarding this amendment, please contact me at:

Phone (813) 866-2299
Fax (813) 975-7757
E-mail julie_townsend@bausch.com

Sincerely,

Julie Townsend

Julie Townsend, MPH
Associate Manager, Regulatory Affairs

ORIGINAL

8500 Hidden River Parkway
Tampa FL 33637
Tel 813 975 7700
www.bausch.com

September 26, 2003

BAUSCH & LOMB

Dianne Tesch, Consumer Safety Officer
Division of Scientific Investigations (HFD-47)
Center for Drug Evaluation and Research
Food & Drug Administration
ATTN: DOCUMENT CONTROL ROOM
7250 Standish Place
Rockville, MD 20855

N. 000(BM)

ORIG AMENDMENT

RE: NDA 21-675
Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3% (Zylet™)
Clinical Study Sites: Response to Request for Information

Dear Ms. Tesch:

Per our conversation on 23 September 2003, this submission contains information regarding the clinical investigational sites used for studies BLP 358-002, BLP 358-003 and BLP 358-006. The following information is included:

- Brief description of each of the three studies
- Investigator Names
- Investigator Site Locations
- Number of patients per site
- Number of patients enrolled / randomized / completed by site
- Count of adverse events per site (counted by All and Treatment Emergent)
- Count of patients with adverse events per site (counted by All and Treatment Emergent)
- Listing of sites discontinued due to non-compliance.

The information contained in this submission is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this submission, please contact me at:

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Fax (813) 975-7757
E-mail julie_townsend@bausch.com

Sincerely,

Julie Townsend

Julie Townsend, MPH
Associate Manager, Regulatory Affairs

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Attachments

cc: Raphael Rodriguez, DAAODP Project Manager