CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20583/S-027

Trade Name: LOTEMAX™

Generic Name: loteprednol etabonate ophthalmic suspension

Sponsor: Bausch & Lomb Pharmaceuticals, Inc.

Approval Date: 10/09/2013

Indication: LOTEMAX is indicated for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20583/S-027

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**x**
Other Action Letters	
Labeling	
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	**x**
Chemistry Review(s)	**x**
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**x**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20583/S-027

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020583/S-027, 020803/S-025, 050804/S-020

APPROVAL LETTER

Bausch & Lomb
Attention: Mary Harrell
Manager Global Pharmaceutical Regulatory Affairs
7 Giralda Farms Suite 1001
Madison, NJ 07940

Dear Ms. Harrell:

Please refer to your Supplemental New Drug Applications (sNDAs) dated March 8, 2013, received March 8, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA NUMBER	SUPPLEMENT NUMBER	PRODUCT NAME
020583	S-027	Lotemax® (loteprednol etabonate ophthalmic suspension)
050804	S-020	Zylet® (loteprednol etabonate and tobramycin ophthalmic suspension)
020803	S-025	Alrex® (loteprednol etabonate ophthalmic suspension)

These "Changes Being Effected in 30 days" supplemental new drug applications provide for the use of an additional ink and varnish system for the drug product applied to the primary container system.

We have completed our review of these supplemental new drug applications. These supplements are approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402-3815.

Sincerely,

{See appended electronic signature page}

Thomas F. Oliver, Ph.D.
Branch Chief, Branch VI
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
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/

THOMAS F OLIVER
10/09/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20583/S-027

MEDICAL REVIEW(S)

Clinical Review of Bundled Changes Being Effected (CBE) Supplements
Supplement

Submission Date: March 8, 2013
Receipt Date: March 8, 2013
Review Date: October 4, 2013

NDA NUMBER	SUPPLEMENT NUMBER	PRODUCT NAME
020583	S-027	Lotemax (loteprednol etabonate ophthalmic suspension) 0.5%
050804	S-020	Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) 0.5%/0.3%
020803	S-025	Alrex (loteprednol etabonate ophthalmic suspension) 0.2%

Applicant: Bausch & Lomb
7 Giralda Farms, Suite 1001
Madison, NJ 07940

Applicant's Representative: Mary E. Harrell
Manager, Global Branded Rx Portfolio
& Regulatory Strategy Group
973-360-6462

Submitted:

Submitted are bundled supplements proposing the use of an additional ink and varnish system for the drug product labels applied to the primary container closure.

Bausch & Lomb makes reference is also made to the supplemental filing (Prior Approval Supplement) of Besivance (besifloxacin hydrochloride ophthalmic suspension) 0.6%, NDA 022308 dated December 20, 2011, and approved April 20, 2012, supporting this same chemistry, manufacturing and controls (CMC) change.

This change is proposed as a Supplement – Changes Being Effected in 30 Days. Bausch & Lomb intends to implement the proposed change 30 days from the date of this submission.

Reviewer's Comments:

These bundled supplements were incorrectly submitted by Bausch & Lomb as Changes Being Effected in 30 Days supplements; inks and varnishes are capable of interacting with the drug product and therefore should have been submitted as Prior Approval supplements.

The applicant has provided a discussion of the rationale for this change, along with supporting data.

Background Discussion:

Bausch & Lomb (B&L) proposes to use an additional ink and varnish system for the drug product labels on the container closure. This is being done to provide manufacturing flexibility and minimize product supply disruption (b) (4) The current and proposed ink systems are provided in the table below.

The proposed ink and varnish system is currently used in Besivance (besifloxacin hydrochloride ophthalmic suspension) 0.6% (NDA 022308). Bausch & Lomb has proposed this change as proposed as a Changes Being Effected 30 Days Supplement in accordance with the *FDA Guidance for Industry: Changes to an Approved NDA or ANDA* (dated 2004), item IX.C.1.a.

The supplier name for the (b) (4) has changed from (b) (4) drug master file (DMF) letters of authorization to access information contained in the supplier's drug master files are provided in this submission. The name of the (b) (4) supplier for the (b) (4) has changed from (b) (4)

There are no changes to the primary packaging components (i.e. bottle, tip, or cap).

Table 1.11.1–1 Summary of changes to label ink and varnish

Current printing method, ink and varnish	Printing method with proposed additional ink and varnish
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)

Reviewer's Comments:

These bundled supplements were incorrectly submitted by Bausch & Lomb as Changes Being Effected in 30 Days supplements; item IX.C.1.a[1]. is incorrectly cited as providing justification. A determination of whether the change in ink and varnish affect the drug product quality can only be made after review of the submitted quality information and supporting data.

Ink Formulations:

Within a given ink system, the ink carrier (or "resin") is generally the same. Individual ink colors within that ink system vary by the specific pigments or dyes mixed with the resin. (b) (4)

[1] A change to or in a container closure system, except as otherwise provided for in this guidance, that does not affect the quality of the drug product.

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

These proprietary formulation data are being shared with US-FDA under explicit consent from (b) (4)

a Excluding individual (b) (4) example.

b Excluding individual (b) (4) example.

Reviewer's Comments:

The components of the current and proposed (b) (4) *are similar.*

Extraction Studies:

A "product presentation extractable" study was performed to further examine the proposed inks for suitability. Test article labels were (b) (4)

(b) (4) were prepared from the current and proposed ink/varnish systems. Labels were applied to (b) (4)

Per B&L, the (b) (4) system demonstrates a minimal extraction profile. Based on the broad HPLC screening assay applied here, it does not introduce any significant new extractables relative to either current ink (whereby "significant" is defined as exceeding the (b) (4) threshold in these product presentation extraction studies). As a further control scheme for any hypothetical leachables not observed in this study, B&L will use (b) (4) specification limit on individual unspecified impurities in drug product assays.

Table 1.11.1–5 Quantitative product presentation extractable results for (b) (4)

(b) (4)

All data represent the average of duplicate samples.

Figure 1.11.1–1 HPLC-UV chromatograms of extractables from (b) (4) **of storage** (b) (4)

(b) (4)

Reviewer's Comments:

The (b) (4)
It does not introduce any significant new extractables (b) (4)

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Stability:

Stability Data have been updated to include 3 months data at long-term condition for commercial scale lots for the three drug products in this bundled supplement (i.e. Lotemax, Zylet, Alrex).

Per the CMC review dated 8/29/2013 for this bundled supplement:

> Results for all the parameters monitored remain well within acceptance criteria for the time reported.
>
> For Lotemax (loteprednol etabonate ophthalmic suspension) 0.5%, Total impurities were found to be 0.7% after 3 months of storage [redacted] (b) (4). For Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) 0.5%/0.3%, Total impurities were found to be 0.8% for [redacted] (b) (4) and 0.3% for [redacted] (b) (4) after 3 months of storage [redacted] (b) (4) For Alrex, (loteprednol etabonate ophthalmic suspension) 0.2%, Total impurities were found to be 1.13% after 3 months of storage [redacted] (b) (4)
>
> These results indicate that the proposed ink/varnish system is compatible, does not contribute any significant new extractable compounds to the final drug product, and that the use of the proposed [redacted] (b) (4) ink/varnish system for the printed labels of the drug product does not have any adverse effect on the final quality of the drug product.

Reviewer's Comments: *Agree.*

Conclusions/Recommendations:

There were no clinical concerns raised with the planned additional ink and varnish system for the drug product labels applied to the primary container closure.

These bundled supplements are recommended for approval; the approval letter is recommended to contain a notation that these bundled supplements should have been submitted as Prior Approval Supplements and not as Changes Being Effected Supplements.

William M. Boyd, M.D.
Clinical Team Leader
Division of Transplant and Ophthalmology Products

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

/s/

WILLIAM M BOYD
10/08/2013

WILEY A CHAMBERS
10/08/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20583/S-027

CHEMISTRY REVIEW(S)

Chemistry Review # 2	**1. Division:** HFD-520	**2. NDA Number:** **20-583**

3. Name and Address of Applicant:
Bausch & Lomb
7 Giralda Farms Suite 1001
Madison, NJ 07940

4. Supplement(s):
Number: S-027
Date(s): March 8, 2013
Stamp Date: March 8, 2013
Due Date; September 8, 2013

5.Name of Drug:
Lotemax®

6. Nonproprietary name:
Loteprednol etabonate ophthalmic suspension, 0.5%

7. Supplement Provides for:
Addition of alternative ink and varnish system for the drug product labels on the container closure.

8. Amendment(s):
None

9. Pharmacological Category:
Anti-inflammatory, corticosteroid

10. How Dispensed:
℞

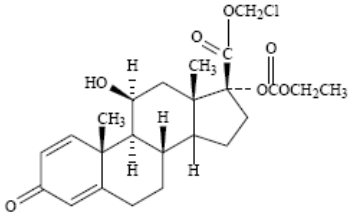
11. Related Documents:
NDA 50-804/S-020, March 8, 2013, Zylet, Loteprednol etabonate and tobramycin suspension, 0.5%/0.3%

NDA 20-803/S-025, March 8, 2013, Alrex® loteprednol etabonate Ophthalmic Suspension, 0.2%

12. Dosage Form:
Ophthalmic Suspension

13. Potency 0.5%

14. Chemical Name and Structure: Loteprednol Etabonate, $C_{24}H_{31}ClO_7$, Mol. Wt. 466.96
Chloromethyl-17⟨-[(ethoxycarbo) oxy]-11®-hydroxy-3-oxandrosta-1, 4-diene-17®-carboxylate.



15. Comments: With this supplement the applicant requests the approval of an additional ink and varnish system for the drug product labels on the container closure. The reasons for this request are to provide manufacturing flexibility and to minimize product supply disruption. (b) (4) This supplement is bundled with supplements NDA 20-803/S025 and NDA 50-804/S-020 for the same change.

The same ink/varnish system change was recently (April 20, 2012) approved for a related drug product from the same applicant in NDA 22-308/S-004, Besivance HCL, Besifloxacin hydrochloride ophthalmic suspension, 0.6%.

These supplements were recommended for **Approval** in Review #1 by the CMC reviewer. However, at the time of completion of the CMC review (August 29, 2013) the clinical review of these supplements had not been completed.

The clinical review is now completed and recommends **Approval** of these supplements. See review in DARRTS, dated October 8, 2013.

16. Conclusions and Recommendations: The CMC and the Clinical reviewers have recommended **Approval** for these bundled supplements. We can now proceed to issue an **Approval (AP)** letter for these applications.

17. Name: **Signature:** **Date:**
Libaniel Rodriguez, Ph.D., Review Chemist

18. Concurrence: **Signature:** **Date:**
Thomas Oliver, Ph.D., Branch Chief, ONDQA/ONDQII/BVI

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

/s/

LIBANIEL RODRIGUEZ
10/09/2013

THOMAS F OLIVER
10/09/2013

Chemistry Review # 1	**1. Division:** HFD-520	**2. NDA Number:** **20-583**

3. Name and Address of Applicant:
Bausch & Lomb
7 Giralda Farms Suite 1001
Madison, NJ 07940

4. Supplement(s):
Number: S-027
Date(s): March 8, 2013
Stamp Date: March 8, 2013
Due Date; September 8, 2013

5.Name of Drug:
Lotemax®

6. Nonproprietary name:
Loteprednol etabonate ophthalmic suspension, 0.5%

7. Supplement Provides for:
Addition of alternative ink and varnish system for the drug product labels on the container closure.

8. Amendment(s):
None

9. Pharmacological Category:
Anti-inflammatory, corticosteroid

10. How Dispensed:
℞

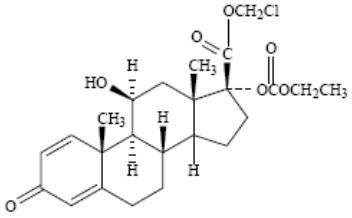
11. Related Documents:
NDA 50-804/S-020, March 8, 2013, Zylet, Loteprednol etabonate and tobramycin suspension, 0.5%/0.3%

NDA 20-803/S-025, March 8, 2013, Alrex® loteprednol etabonate Ophthalmic Suspension, 0.2%

12. Dosage Form:
Ophthalmic Suspension

13. Potency 0.5%

14. Chemical Name and Structure: Loteprednol Etabonate, $C_{24}H_{31}ClO_7$, Mol. Wt. 466.96
Chloromethyl-17⟨-[(ethoxycarbo) oxy]-11®-hydroxy-3-oxandrosta-1, 4-diene-17®-carboxylate.



15. Comments: With this supplement the applicant requests the approval of an additional ink and varnish system for the drug product labels on the container closure. The reasons for this request are to provide manufacturing flexibility and to minimize product supply disruption. (b) (4) This supplement is bundled with supplements NDA 20-803/S025 and NDA 50-804/S-020 for the same change.

The same ink/varnish system change was recently (April 20, 2012) approved for a related drug product from the same applicant in NDA 22-308/S-004, Besivance HCL, Besifloxacin hydrochloride ophthalmic suspension, 0.6%.

This proposed change involves the label ink sub-part of the Module 3, section 3.2.P 7, Container Closure System only. All other aspects of the Container Closure System remain unchanged.

The following information and data were provided in support of the proposed change:

- Review of ink formulation, direct solvent extraction screening and confirmatory product-presentation extractable test for both, the current and the proposed ink systems..
- Three months of stability data at the long term (25°C/40% RH) storage conditions for two batches of Loteprednol etabonate Ophthalmic Suspension, 0.5% drug product manufactured and tested at the Bausch & Lomb manufacturing facility in Tampa, Florida, USA, and using labels printed with the proposed ink and varnish system.

Details of the information and data provided are discussed in the Chemistry Review Notes section of this review, below.

16. Conclusions and Recommendations: The comparative information and data provided for the components of the current and proposed ink/varnish systems indicate that the proposed (b) (4) ink/varnish system is equivalent to the current system. It also indicates that the proposed system is compatible, does not contribute any significant new extractable compounds to the final drug product, and its use in the printed labels does not have any adverse effect on the final quality of the drug product. From the point of view of CMC, this supplement is recommended for **approval**.
17. Name: **Signature:** **Date:** **Libaniel Rodriguez, Ph.D., Review Chemist**
18. Concurrence: **Signature:** **Date:** **Thomas Oliver, Ph.D., Branch Chief, ONDQA/ONDQII/BVI**

13 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Comment: Results for all the parameters monitored remain well within acceptance criteria for the time reported.

For Lotemax®, Loteprednol etabonate ophthalmic suspension, 0.5%, Total impurities were found to be 0.7% after 3 months of storage (b) (4) For Zylet®, Loteprednol etabonate and tobramycin ophthalmic suspension, 0.5%/0.3%, Total impurities were found to be 0.8% for (b) (4). and 0.3% for (b) (4) after 3 months of storage (b) (4) and for Alrex®, Loteprednol etabonate ophthalmic suspension, 0.2%, Total impurities were found to be 1.13% after 3 months of storage (b) (4)

These results indicate that the proposed ink/varnish system is compatible, does not contribute any significant new extractable compounds to the final drug product, and that the use of the proposed (b) (4) ink/varnish system for the printed labels of the drug product does not have any adverse effect on the final quality of the drug product.

Conclusion: The comparative information and data provided for the components of the current and proposed ink/varnish systems indicate that the proposed (b) (4) ink/varnish system is equivalent to the current system. It also indicates that the proposed system is compatible, does not contribute any significant new extractable compounds to the final drug product, and that its use in the printed labels does not have any adverse effect on the final quality of the drug product. From the point of view of CMC, this supplement is recommended for **approval**.

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

/s/

LIBANIEL RODRIGUEZ
08/29/2013

THOMAS F OLIVER
08/29/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20583/S-027

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020583/S-027, NDA 050804/S-020, NDA 020803/S-025

CBE SUPPLEMENT – ACKNOWLEDGEMENT

Bausch & Lomb
Attention: Mary Harrell
Manager Global Pharmaceutical Regulatory Affairs
7 Giralda Farms Suite 1001
Madison, NJ 07940

Dear Ms. Harrell:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER	SUPPLEMENT NUMBER	PRODUCT NAME
020583	S-027	Lotemax® (loteprednol etabonate ophthalmic suspension)
050804	S-020	Zylet® (loteprednol etabonate and tobramycin ophthalmic suspension)
020803	S-025	Alrex® (loteprednol etabonate ophthalmic suspension)

DATE OF SUBMISSION: 3/8/2013

DATE OF RECEIPT: 3/8/2013

This supplemental application, submitted as ”Changes Being Effected in 30 days” supplement, proposes the following change(s): additional ink and varnish system for drug product labels.

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 5/7/2013 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be 9/8/2013.

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthamology
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call Althea Cuff, Regulatory Project Manager, at (301) 796 – 4061.

Sincerely,

{See appended electronic signature page}

Althea Cuff
Regulatory Project Manager
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
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/

ALTHEA CUFF
04/08/2013