CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-804 (formerly 21-675)

Chemistry Review(s)

Food & Drug Administration

Memorandum

Date : November 29, 2004

From: Linda Ng, Ph.D.,
Chemistry Team Leader, HFD-550

Subject: Labeling Comments for NDA 21-675, Zylet(loteprednol etabonate and tobramycin ophthalmic suspension) 0.5%/0.3%, Bausch and Lomb

To: The File

Content
This memo is to address the labeling comments from a chemistry, manufacturing and controls perspective. The comments cover the package insert, immediate and package labels.

1. Under the Description section of the package insert, 3rd line, replace the underline comment with "Both loteprednol etabonate and tobramycin are white to off-white powders." This is consistent with previously approved single drug substance products.

2. Under the How Supplied section of the package insert, "Use only if imprinted neckband is intact" is recommended to replace [ ]

3. Agree with Medical team leader, Dr. Boyd's comments:

On all the submitted container labels and cartons, storage should be revised to read:

Storage: Store upright at 15°-25° C (59°-77° F). PROTECT FROM FREEZING.

All submitted cartons should be revised to read:

Each mL contains: Actives: Loteprednol Etabonate 5 mg (0.5%) and Tobramycin 3 mg (0.3%). Inactives: Edetate Disodium, Glycerin, Povidone, Purified Water, Tyloxapol, and Benzalkonium Chloride 0.01% (preservative). Sulfuric Acid and/or Sodium Hydroxide may be added to adjust the pH to 5.7-5.9. The suspension is essentially isotonic with a tonicity of 250 to — mOsm/kg.

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/s/

Linda Ng
11/29/04 02:20:12 PM
CHEMIST
Comments for the final proposed NDA labeling

Chemistry Review Data Sheet

1. NDA 21-675

2. REVIEW #: 2

3. REVIEW DATE: 5/14/04

4. REVIEWER: Su C. Tso

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Presubmission	7/21/03
Original	9/8/03
Amendment	11/26/03
Amendment	3/2/04

6. SUBMISSION(S) BEING REVIEWED:

Amendment dated 4/13/04, 4/21/04, and 5/10/04

7. NAME & ADDRESS OF APPLICANT:

Name: Bausch & Lomb

Address: 8500 Hidden River Parkway, Tampa, FL 33637

Representative: Julie Townsend, MPH

Telephone: 813-866-2299

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zylet
b) Non-Proprietary Name (USAN): loteprednol Etabonate and Tobramycin
c) Code Name/# (ONDC only): n/a
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: S

Trade name is approved by DMETS and DDMAC under IND 36,209 (attachment 5).

9. LEGAL BASIS FOR SUBMISSION:

Pursuant to 21 CFR 314.54 and section 505 (b) of the Federal Food, Drug, and Cosmetic Act, Bauch & Lomb submitted new drug application NDA 21-675. The drug product, Loteprednol and Tobramycin, 0.5% /0.3%, Ophthalmic Suspension, will be marketed as a prescription drug by Bausch & Lomb. The application is based upon evidence of safety and effectiveness in the treatment of inflammatory ocular conditions where the risk of bacterial infection exists. The drug product is classified as 4S.

10. PHARMACOL. CATEGORY: Anti-inflammatory and anti-bacterial

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 0.5%/0.3%

13. ROUTE OF ADMINISTRATION: Topical/Ocular, 1-2 drops in the affected eye every 4-6 hours

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

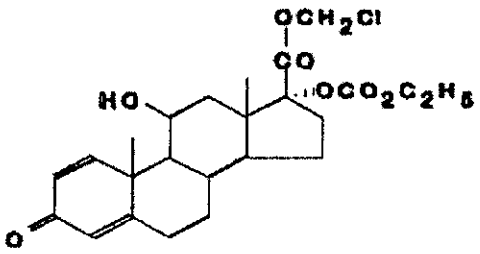
One of the active drug substances, tobramycin, is manufactured by L J

__x__SPOTS product – Form Completed for the manufactured of Tobramycin by L J

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR EEIGHT

Loteprednol Etabonate

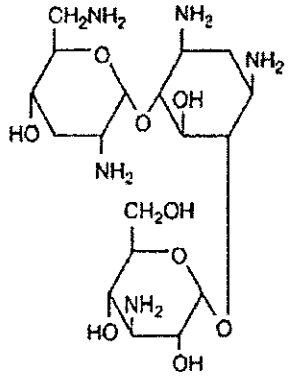
- CAS No. 82034-46-6
- Chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β carboxylate



$C_{24}H_{31}ClO_7$
Formula Weight = 466.96
White amorphous solid
Melting point – decomposes at ~232°C
No known isomers or polymorphs; no ionizable group

Tobramycin

- CAS No. 32986-56-4
- O-3-Amino-3-deoxy- α -D-glucopyranosyl-(1→4)-O- [2,6-diamino-2,3,6-trideoxy- α -D-*ribo*-hexopyranosyl-1(1→6)] -2-deoxy-streptamine



$C_{18}H_{37}N_5O_9$
Formula Weight = 467.52
White to off-white powder

17. RELATED/SUPPORTING DOCUMENTS:

Executive Summary Section

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Loteprednol Etabonate	3 1	Adequate	8/29/95 & 3/4/97 11/7/03	Sid Gilman, # 1 & # 2 Su Tso, # 3
	II		Tobramycin	3 3 1	Adequate Adequate Adequate	2/1/01& 7/31/02 10/31/03	Maria Shih, #6 Yanping Pan, #7 Su Tso, #8
	II		Tobramycin	3 1	Adequate Adequate	1/30/02 10/17/03	Yanping Pan, #5 Su Tso# 6
	III			1	Adequate	10/5/00 & 3/1/02	L. Rodriguez & Yong-de Lu
	III			1	Adequate	9/12/03	S. Tso, #4
	III			3 1	Adequate Adequate	11/8/96 & 7/22/99 10/22/03	S. Tso & Raj Uppoor S. Tso, # 6
				3	Adequate	10/13/93	A. Mueller
	III			1	Adequate	9/15/03	S. Tso, #1
	III			3	Adequate	4/22/98	Arthur Shaw #2

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 - DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application; therefore the DMF did not need to be reviewed).

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	36,209, Bausch & Lomb	Loteprednol Etabonate and Tobramycin
IND	32,432, Bausch & Lomb	Loteprednol Etabonate
NDA	20-583, Bausch & Lomb	Lotemax, Loteprednol etabonate ophthalmic suspension, 0.5%
NDA	20-803, Bausch & Lomb	Alrex, Loteprednol Etabonate Ophthalmic Suspension, 0.2%
NDA	50-541, Falcon	Tobrex, Tobramycin Ophthalmic Solution, USP 0.3%
ANDA	64-052, Bausch & Lomb	Tobramycin Ophthalmic Solution, USP 0.3%

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	Acceptable	2/27/04	S. Adam
Pharm/Tox	Approval	12/19/03	Asoke Mukherjee
Biopharm	n/a		
DMETS DDMAC	Approval	1/23/04	Jerry Phillips
Methods Validation	Revised methods acceptable. These methods will not submitted to FDA laboratory for validation	5/14/04	S. Tso
EA	Category exemption accepted		S. Tso
Microbiology	Approval	10/24/03	Paul Stinavage

The Chemistry Review for NDA 21-675

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval from a chemistry, manufacturing, and control standpoint. All manufacturing sites are in cGMP compliance.

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

None

II. Summary of Chemistry Assessments

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

Loteprednol etabonate is a white amorphous solid with a melting point an approximately 232 °C with decomposition, no known isomer or polymorph, and no ionizable group. Loteprednol etabonate will be manufactured and supplied by [ ](DMF [ ] Loteprednol etabonate is an approved drug substance for NDA 20-583 and NDA 20-803.

Tobramycin is a white to off white powder. It is an approved drug substance for NDA 50-541 and ANDA 64-052. Tobramycin will be manufactured and supplied by [ ] [ ]

The drug product is a combination drug of loteprednol etabonate and tobramycin, 0.5%/0.3%. The finished dosage form is a sterile white to off-white suspension. It is preserved with a 0.01% benzalkonium chloride. Other inactive ingredients include edetate disodium dihydrate [ ], glycerin [ ] providone [ ] [ ], and tyloxapol [ ] The formulation is adjusted to pH [ ] The formulation contains the same ingredients as that of NDA 20-583 with the exception of tobramycin. The suspension is packaged in a white low density polyethylene bottle with a white [ ] tip and white polypropylene cap. The fill sizes include 2.5 mL and 5 mL packaged in a 7.5 mL bottle, and a 10 mL packaged in a 10 mL bottle. The product will be manufactured at Bausch & Lomb, Tampa, FL.

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

The drug product is indicated for steroid-response inflammatory conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. The recommended dose is 1-2 drop in the affected eye every 4-6 hours.

The product may be approved with an expiration date of 24 months when stored at 15-25 °C for all trade sizes. There is no physician sample.

C. Basis for Approvability or Not-Approval Recommendation

The drug product composes of 0.5% loteprednol etabonate and 0.3% tobramycin with inactive ingredients being edetate disodium dehydrate, glycerin, povidone, and tyloxapol. The dosage form is demonstrated to be stable for 24 months under ambient temperature by stability data. Container/closure components were adequately described and qualified. Drug substance and drug product specification are adequate, analytical control procedures are in place at the manufacturing site to ensure quality of the drug product.

The application is recommended for approval from chemistry, manufacturing, and control standpoint. The recommended expiration dates are 24 months when stored under 15-25 °C for all trade sizes.

III. Administrative

A. Reviewer's Signature :

Su C. Tso

B. Endorsement Block

Chemist/Tso/5-14
-04
ChemistryTeamLeader./Ng
Project Manager/Rodriguez

C. CC Block

14 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Su Tso
5/17/04 09:42:49 AM
CHEMIST

Linda Ng
5/17/04 10:46:12 AM
CHEMIST
CMC recommends approval

NDA 21-675

Zylet
Loteprednol Etabonate and Tobramycin
0.5%/0.3%

Bausch & Lomb

Su C. Tso, Ph. D.

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

HFD-550

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-675

2. REVIEW #: 1

3. REVIEW DATE: 4/19/04

4. REVIEWER: Su C. Tso

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 32,432	Loteprednol and Tobramycin Suspension, 2/1/91
IND 36,209	Loteprednol Etabonate Suspension, 9/22/89

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Presubmission	7/21/03
Original	9/8/03
Amendment	11/26/03
Amendment	3/2/04

7. NAME & ADDRESS OF APPLICANT:

Name: Bausch & Lomb

Address: 8500 Hidden River Parkway, Tampa, FL 33637

Representative: Julie Townsend, MPH

Telephone: 813-866-2299

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zylet
b) Non-Proprietary Name (USAN): loteprednol Etabonate and Tobramycin
c) Code Name/# (ONDC only): n/a
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: S

Trade name is approved by DMETS and DDMAC under IND 36,209 (attachment 5).

9. LEGAL BASIS FOR SUBMISSION:

Pursuant to 21 CFR 314.54 and section 505 (b) of the Federal Food, Drug, and Cosmetic Act, Bauch & Lomb submittednew drug application NDA 21-675. The drug product, Loteprednol and Tobramycin, 0.5% /0.3%, Ophthalmic Suspension, will be marketed as a prescription drug by Bausch & Lomb. The application is based upon evidence of safety and effectiveness in the treatment of inflammatory ocular conditions where the risk of bacterial infection exists. The drug product is classified as 4S.

10. PHARMACOL. CATEGORY: Anti-inflammatory and anti-bacterial

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 0.5%/0.3%

13. ROUTE OF ADMINISTRATION: Topical/Ocular, 1-2 drops in the effected eye every 4-6 hours

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

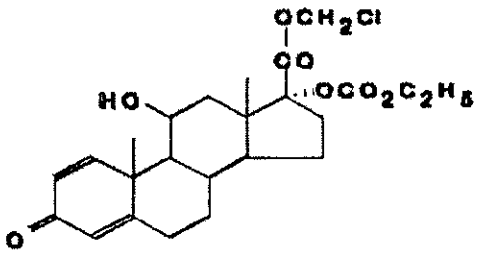
One of the active drug substances, tobramycin, is manufactured by [redacted]

__x__SPOTS product – Form Completed for the manufactured of Tobramycin by [redacted]

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR EEIGHT

Loteprednol Etabonate

- CAS No. 82034-46-6
- Chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β carboxylate



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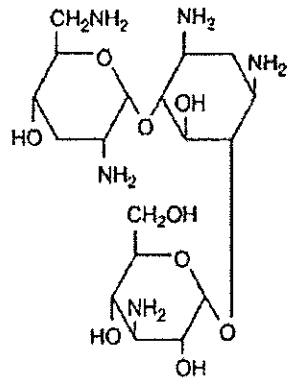
Tobramycin

- CAS No. 32986-56-4
- *O*-3-Amino-3-deoxy- α -D-glucopyranosyl-(1→4)-*O*- [2,6-diamino-2,3,6-trideoxy- α -D-*ribo*-hexopyranosyl-1(1→6)] -2-deoxy-streptamine



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	II		Tobramycin	3 3 1	Adequate Adequate Adequate	2/1/01& 7/31/02 10/31/03	Maria Shih, #6 Yanping Pan, #7 Su Tso, #8
	II		Tobramycin	3 1	Adequate Adequate	1/30/02 10/17/03	Yanping Pan, #5 Su Tso# 6
	III			1	Adequate	10/5/00 & 3/1/02	L. Rodriguez & Yong-de Lu
	III			1	Adequate	9/12/03	S. Tso, #4
	III			3 1	Adequate Adequate	11/8/96 & 7/22/99 10/22/03	S. Tso & Raj Uppoor S. Tso, # 6
				3	Adequate	10/13/93	A. Mueller
	III			1	Adequate	9/15/03	S. Tso, #1
	III			3	Adequate	4/22/98	Arthur Shaw #2

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1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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7 - Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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NDA	50-541, Falcon	Tobrex, Tobramycin Ophthalmic Solution, USP 0.3%
ANDA	64-052, Bausch & Lomb	Tobramycin Ophthalmic Solution, USP 0.3%

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	Acceptable	2/27/04	S. Adam
Pharm/Tox	Approval	12/19/03	Asoke Mukherjee
Biopharm	n/a		
DMETS DDMAC	Approval	1/23/04	Jerry Phillips
Methods Validation	Delayed until revision received and reviewed from the firm		S. Tso
EA	Category exemption accepted		S. Tso
Microbiology	Approval	10/24/03	Paul Stinavage

The Chemistry Review for NDA 21-675

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable from a chemistry, manufacturing, and control standpoint pending for a satisfactory response to the chemistry deficiencies dated 3/25/04 (attachment 4). All manufacturing facilities are in cGMP compliance as of 2/27/04 (attachment 8)

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

none

II. Summary of Chemistry Assessments

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

Loteprednol etabonate is a white amorphous solid with a melting point an approximately 232 °C with decomposition, no known isomer or polymorph, and no ionizable group. Loteprednol etabonate will be manufactured and supplied by [ ] (DMF [ ]), [ ] Loteprednol etabonate is an approved drug substance for NDA 20-583 and NDA 20-803.

Tobramycin is a white to off white powder. It is an approved drug substance for NDA 50-541 and ANDA 64-052. Tobramycin will be manufactured and supplied by [ ]

The drug product is a combination drug of loteprednol etabonate and tobramycin, 0.5%/0.3%. The finished dosage form is a sterile white to off-white suspension. It is preserved with a 0.01% benzalkonium chloride. Other inactive ingredients include edetate disodium dehydrate [ ] glycerin [ ], providone [ ] and tyloxapol [ ] The formulation is adjusted to pH [ ] The formulation contains the same ingredients as that of NDA 20-583 with the exception of tobramycin. The suspension is packaged in a white low density polyethylene bottle with a white [ ] tip and white polypropylene cap. The fill sizes include 2.5 mL and 5 mL packaged in a 7.5 mL bottle, and a 10 mL packaged in a 10 mL bottle. The product will be manufactured at Bausch & Lomb, Tampa, FL.

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

The drug product is indicated for steroid-response inflammatory conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. The recommended dose is 1-2 drop in the affected eye every 4-6 hours.

The product may be approved with an expiration date of 24 months when stored at 15-25 °C

C. Basis for Approvability or Not-Approval Recommendation

The drug product composes of 0.5% loteprednol etabonate and 0.3% tobramycin with *inactive ingredients being* edetate disodium dehydrate, glycerin, povidone, and tyloxapol. The dosage form is demonstrated to be stable for 24 months under ambient temperature by stability data. Container/closure components were adequately described. However due to the last change of [ ] in the label, compatibility of the new [ ] system with the drug product must be demonstrated by stability data of the validation batches. Although analytical control procedures are in place at the manufacturing site to ensure quality of the drug product, but the methods have to be modified for clarity. In addition, the drug substance and product specifications have to be revised.

The application is therefore approvable from chemistry, manufacturing, and control standpoint pending a satisfactory resolution of chemistry deficiencies listed in fax dated 3/30/04 (attachment 4).

III. Administrative

A. Reviewer's Signature :

Su C. Tso

B. Endorsement Block

Chemist/Tso/4-16-04
ChemistryTeamLeader./Ng
Project Manager/Rodriguez

C. CC Block

56 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Su Tso
4/28/04 02:44:40 PM
CHEMIST

Linda Ng
4/29/04 12:01:35 PM
CHEMIST

NDA 21-675

Zylet
Loteprednol Etabonate and Tobramycin
0.5%/0.3%

Bausch & Lomb

Su C. Tso, Ph. D.

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

HFD-550

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