CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-134

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 5

2. ANDA # 64-134

3. NAME AND ADDRESS OF APPLICANT
Bausch & Lomb
Pharmaceutical Division
8500 Hidden River Parkway
Tampa, FL 336378

4. LEGAL BASIS FOR SUBMISSION
Reference drug: TobraDex® (NDA #50-592, approved 8/18/88) manufactured by Alcon.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME
Tobramycin and Dexamethasone Ophthalmic Suspension USP, 0.3%/0.1%

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

1.	Original submission	7/29/94
2.	Letter indicating intention to file requisite Bio study data and requesting meeting with Division of Bioequivalence	9/21/94
3.	Bioequivalence protocol	10/6/94
4.	Biostudy and CMC amendments	8/31/95
5.	Gratuitous Amendment - additional impurity information	11/17/95
6.	Major amendment	6//11/96
7.	Proposed bio protocol	8/19/96
8.	Telephone amendment regarding process validation data for sterility assurance	12/4/96
9.	Response to 6/6/96 bio deficiency letter	2/14/97
10.	Bioequivalence amendments	4/4/97, 4/9/97 & 4/15/97
11.	Chemistry amendment	5/16/97
12.	Gratuitous amendment	6/23/97
13.	Bioequivalence amendment	7/1/97

15. Chemistry amendment 12/10/98
16. Chemistry amendments 8/10/99 and 8/18/99 (this review)
17. Labeling amendment 9/3/99
18. Micro amendment 9/9/99

FDA:

1.	Refuse to file letter		8/22/94
2.	Response to request for a meeting		9/30/95
3.	Acknowledgment of receipt of application		10/23/95
4.	Medical officer review (Chambers):	**N/A**	3/24/96
5.	Microbiology review #1	unacceptable	2/2/96
6.	Bioequivalence review:	unacceptable	6/6/96
7.	Labeling review #1:	unacceptable	1/18/96
8.	Chemistry review#1	unacceptable	3/12/96
9.	Labeling review:	**acceptable**	6/19/96
10.	EER:	**acceptable**	6/10/96
11.	Sample evaluation:	**acceptable**	6/18/96
12.	Notice of denial of request for a meeting and comments about timing of review of proposed protocol		9/5/96
13.	Microbiology review #2:	**acceptable**	11/27/96
14.	Chemistry review #2	unacceptable	12/17/96
15.	Deficiency letter #2		12/27/96
16.	Bio deficiency letter #2		9/19/97
17.	Chemistry review #3 (unacceptable)		LETTER 11/17/97
18.	Bio acceptable 6/17/99		
19.	Chemistry review #4 (unacceptable)		FAX 7/26/99

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
See under #37 DMF CHECKLIST

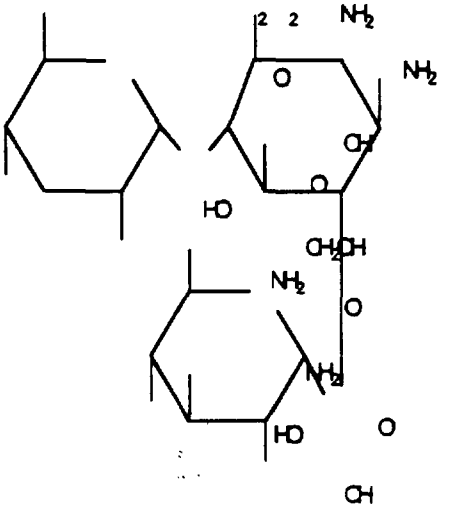
13. DOSAGE FORM
Ophthalmic Suspension

14. POTENCY
0.3%/0.1%

15. CHEMICAL NAME AND STRUCTURE

Tobramycin USP

$C_{18}H_{37}N_5O_9$; M.W. = 467.52

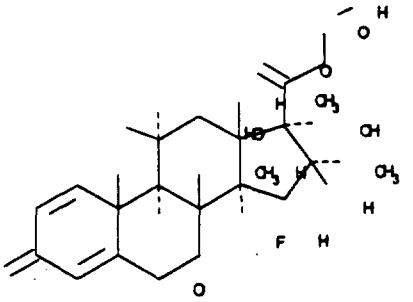


o-3-Amino-3- deoxy-a-D-glucopyranosyl-(164)-o-[2,6-diamino-2,3,6-trideoxy-a-D-ribo-hexopyranosyl-(166)]-2-deoxy-L-streptamine

CAS [32986-56-4]

Dexamethasone USP

$C_{22}H_{29}FO_5$; M.W. = 392.47



9-Fluoro-11ß,17,21-trihydroxy-16a-methylpregna-1,4-diene-3,20-dione. CAS [50-02-2]

16. RECORDS AND REPORTS N/A

17. COMMENTS

This application was originally reviewed by R. Adams (three reviews) and reassigned to me 7/99.

First generic application for this drug product.
Specifications for innovator Alcon's TobraDex® is provided in this review.

In FAX AMENDMENT 8/10/99, Firm responds in order:

Regarding bulk material submit Tobramycin:

Q1a. Please submit a copy of COA for Tobramycin Lot #0926897 from bulk manufacturer Biogal.

A1a. Firm clarifies some concerns regarding the lot number and a copy of Biogal's COA is enclosed.

Comments:

Under Results for "related substances" (our concerns for the last review #4), no actual results were given except the description for Specification.

Call was made to B&L (see memo dated 8/17/99). Firm agrees to provide analytical data with actual results on Biogal material. In Telephone/Facsimile amendment 8/18/99 Firm includes COAs (from both Biogal and B&L) on three lots. Results for "related substances" are summarized as follows:

(#1 Biogal lot#TO-50398 - B&L lot#0104199
#2 Biogal lot#TO-40698 - B&L lot#0104099
#3 Biogal lot#TO-02298 - B&L lot#0103999)

Related Substances	Limits % Biogal/B&L	Results (Bio/B&L)% #1	#2	#3
Neamine		<0.1/0.1	<0.03/0.0	<0.03/0.0
Kanamycin		<0.03/0.0	<0.1/0.0	0.11/0.1
Nebramine		<0.1/0.0	<0.1/0.0	<0.1/0.0
Total		0.7/0.2	0.6/0.2	0.8/0.2

Firm's comments: 1) The values reported by Biogal are not significantly different than those determined by B&L.
2) Although the acceptance limits set by Biogal are wider than those by B&L, Firm will continue to impose their own specifications on this material and reject lots which do not meet their specifications. **Acceptable**

Q1b. It is not clear about the pH result for Lot #0926897 on page 96. Please clarify.

A1b. Firm states that the result is a pH of solution" which passes the specification

Acceptable

Q2. We note from the stability reports that dexamethasone content fails the potency limit at several test stations when samples were stored inverted. Please comment.

A2. Firm states that the dexamethasone potency failure is attributed to the retention of the suspended active ingredient in the container tip during inverted storage. This retention of the active ingredient may prevent adequate resuspension, resulting in low assay values. Firm states that this is a purely physical phenomenon and is not a reflection on drug product integrity as it pertains to the stability of the active ingredients (s). In their development studies conducted in horizontal orientation have indicated no non-conformances for the potency value for dexamethasone. A summary of the assay data for both upright and horizontal orientations in Table 1 demonstrates the conformance at 0, 10, 20, 30, 60 and 90 days for both active ingredients.

Comments:

It is not clear why innovator specifies "upright storage" on their labeling. By suggestion of our Labeling Chief Charlie Hoppes, I called for Reference Drug TobraDex®. **She said most of their suspension products recommend upright storage. So far their stability studies include only samples stored upright for all their products.** They are now making commitments to subject product samples at both orientations (inverted and upright). Supplements regarding this issue are being submitted to FDA for approval. She said this eye suspension product uses small container tip, when inverted, dexamethasone (insoluble) might deposit in the tip and might be hard to get back into suspension when it is dried. In her opinion, this situation should not happen when the eye product is carried around in the pocket or purse, if it is used daily and well shaken before use during the two-week prescription time.

It appears that we OGD require stricter stability standards (we require samples for suspension, lotion, cream, solution, etc. be stored upright, horizontal, and inverted). In this case, B&L's response is adequate and we should let it go based on Innovator's experiences.

Status Summary for #64-134:

DMFs:

Labeling:	Satisfactory (9/13/99)
EER:	Pending
Sample:	Not requested (USP drug)
Bio:	Acceptable 6/17/99
Micro:	Acceptable 11/27/96; see also reviews done by C. Vincent 5/10/99 and L. Ensor 9/10/99.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended

19. REVIEWER: Maria C. Shih — DATE COMPLETED: 8/20/99

Page(s) 12

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chem Rev 5

8/20/99