



SEP 14 1997

Tobramycin and Dexamethasone      Bausch & Lomb Pharmaceuticals  
Ophthalmic Suspension, USP      Tampa, FL  
0.3%/0.1%      Submission Date:  
AADA #64-134      February 14, 1997  
Reviewer: Moheb H. Makary  
WP. 64134S.297

Review of a Consultative Review of Clinical Bioequivalence Study

Introduction:

Tobramycin and Dexamethasone Ophthalmic Suspension is a sterile, multiple dose antibiotic and steroid combination for topical ophthalmic use. It 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. The listed reference drug product is Tobradex<sup>R</sup> Ophthalmic Suspension 0.3%/0.1% manufactured by Alcon Laboratories.

The firm had previously submitted an unacceptable clinical study: comparing the bioequivalence of Tobradex<sup>R</sup> with the Bausch & Lomb's Tobramycin and Dexamethasone Ophthalmic Suspension in human aqueous humor (submission dated August 31, 1995).

The firm has submitted this clinical study, wherein, bioequivalence was evaluated based on two critical parameters; conjunctive injection and itching in addition to the comparison of representative Kill Curve (microbial analysis) for Bausch & Lomb (BLP)'s Tobramycin and Dexamethasone Ophthalmic Suspension and Alcon's Tobradex<sup>R</sup>.

The submission was sent to HFD-550 for consult.

Review Comments by The Medical Officer

1. For the conjunctive injection parameter, the results demonstrated that there is clear separation between the placebo groups and the steroid/antibiotic groups. The results also indicate that the reproducibility at the different time points is considered sufficient in this case to establish equivalency with respect to one of the critical parameters (conjunctive injection).
2. For the itching parameter, the results indicated that while the Tobradex<sup>R</sup> (reference product) demonstrates a difference from the placebo groups, the test product (BLP), does not demonstrate a consistent pattern.
3. Regarding the comparison of representative Kill Curve

(microbial analysis), the results indicated that all bacterial culture except C. Albicans and A. Niger demonstrated 0% survival for all time points for both RLD and BLP. The values for C. Albicans and A. Niger were equivalent between groups.

4. In summary, the study fails to demonstrate bioequivalence because of the inability to demonstrate equivalence with respect to itching. The study therefore is inconsistent with respect to the major parameters.

**Medical Officer's Conclusions:**

"The study results are confusing. Evidence of effectiveness and bioequivalence appears to exist with respect to the conjunctive injection parameter, but not with the itching parameter. These two signs/symptoms define the measurable allergic response in the eye and while different pharmacologic agents have different effects on each, corticosteroids are well known to be effective in each. The clear differences seen with respect to conjunctive injection should also have been observed with itching. Although the Tobradex<sup>R</sup> performs better than the test formulation, it too, did not perform as well as expected. It is more likely that this represent a failed study than true inequivalence".

**Recommended Regulatory Action:**

Bioequivalence cannot be supported at this time.

The firm should be informed of the above recommendation.

*Moheb H. Makary*

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Tobramycin and Dexamethasone    Bausch & Lomb Pharmaceuticals  
Ophthalmic Suspension, USP      Tampa, FL  
0.3%/0.1%                              Submission Date:  
AADA #64-134                            August 31, 1995  
Reviewer: Moheb H. Makary  
WP. 64134S.895

Review of a Consultative Review of Clinical Bioequivalence Study

Introduction:

Tobramycin and Dexamethasone Ophthalmic Suspension is a sterile, multiple dose antibiotic and steroid combination for topical ophthalmic use. It 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. The listed reference drug product is Tobradex<sup>®</sup> Ophthalmic Suspension 0.3%/0.1% manufactured by Alcon Laboratories.

This AADA contains a clinical study comparing the bioequivalence of Tobradex<sup>®</sup> versus the Bausch & Lomb's Tobramycin and Dexamethasone Ophthalmic Suspension in human aqueous humor. Bioequivalence was evaluated based on the concentration of dexamethasone of each drug in the aqueous humor after a single dose prior to cataract surgery. The comparison of representative Kill Curve (microbial analysis) for Bausch & Lomb's Tobramycin and Dexamethasone Ophthalmic Suspension and Alcon's Tobradex<sup>®</sup> was performed and submitted.

The submission was sent to HFD-550 for consult.

Review Comments by The Medical Officer

1. The firm based the protocol design on discussions with the agency. In response to the firm's proposal, the agency noted that the statistical methods to assess equivalence had not been included and that these methods should be specified. The protocol did not include an adequate description of the statistical methods. Specifically, the rationale for the number of subjects, the power to detect a clinically meaningful difference and the difference to be ruled out were not included. The method proposed, t-test, is based on an assumption of a normal distribution. This is a valid assumption, but it was not achieved in the results.

2. The assay methodology of aqueous humor specimens were to undergo a

..... This is a relatively new methodology and its validation is unclear.

1. All organisms listed in the USP Preservative effectiveness test
2. All organisms listed in the Indications section of Tobradex.

The inoculated product samples should be quantified for surviving viable bacteria (in CFU/mL) after 30, 60, 120, 240 and 360 minutes of contact time. The testings should be performed at least twice.

Recommendations:

1. While differences in physical parameters have been noted, the differences are considered immaterial if clinical bioequivalence can be determined by clinical testing or by adequate comparisons of aqueous humor levels. The small number of subjects, the unexpectedly large variability, the assay reproducibility and the deviation from normality are significant flaws in reported results of this study. The original protocol designed assumed normality and clinical expectations would predict normality.

The data from this study alone cannot be used to assess bioequivalence.

2. There is a clear misunderstanding by the firm of testing methodology. The test performed provides no useful information concerning the effect of this particular formulation on the killing rate of the microorganisms listed for the product.

The firm should perform in vitro "kill rate" studies comparing Tobradex to their proposed tobramycin-dexamethasone formulation.

Each formulation should be challenged with approximately  $5 \times 10^4$  CFU/mL of each of the following panel of microorganisms in order to compare their antibacterial kill rates:

1. All organisms listed in the USP Preservative effectiveness test
2. All organisms listed in the Indications section of Tobradex.

The inoculated product samples should be quantified for surviving viable bacteria (in CFU/mL) after 30, 60, 120, 240 and 360 minutes of contact time. The testings should be performed at least twice.

Recommended Regulatory Action:

Bioequivalence cannot be supported at this time.

3. Patients had a second assay because their results were found to lie in the area of non-linearity. The differences between the original and "re-assay" are significant and call into question the assay methodology and reproducibility.

4. Forty-three (43) patients were enrolled in the study, of which 40 (23♀, 17♂, all white) contributed aqueous humor and were assayed. Patients had aqueous humor collected outside the ± 5 minute timeframe. Patient had insufficient quantity of aqueous collected. Assays should have been performed on all subjects for which there was a valid sample (i.e., regardless of the time period). The firm failed to include any non-white subjects and failed to record iris color. These are significant deficiencies.

5. The data analysis of the dexamethasone concentration results revealed that the data is non-normal. For this reason the firm used the Wilcoxon Rank Sum Test to test for treatment group differences. The number of subjects studied is small and the variability is unexpectedly large. The departure from normality in this case cannot be handled by statistical means. The original protocol designed assumed normality and clinical expectations would predict normality. The data from this study alone cannot be used to assess bioequivalence.

6. The particle sizes of Dexamethasone for the firm test product and Tobradex<sup>®</sup> reference product are different however, differences observed should be considered irrelevant if clinical bioequivalence is established by clinical test results or by aqueous humor levels.

7. The drop volume delivered from the test product in comparison to the reference product volume appears different. However, the differences observed should be considered irrelevant if clinical bioequivalence is established by clinical test results or by aqueous humor levels.

8. The anti-bacterial activity of the tobramycin in both the test and reference products was determined by the microbial kill curves for a range of organisms. There is a clear misunderstanding by the firm of testing methodology. The test performed provides no useful information concerning the effect of this particular formulation on the killing rate of the microorganisms listed for the product.

The applicant should perform in vitro "kill rate" studies comparing Tobradex to their proposed tobramycin-dexamethasone formulation.

Each formulation should be challenged with approximately  $5 \times 10^4$  CFU/mL of each of the following panel of microorganisms in order to compare their antibacterial kill rates:

The firm should be informed of the above recommendations.

*Moheb H. Makary*

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4/24/96