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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-804 (formerly 21-675)

Clinical Pharmacology and Biopharmaceutics Review

12/7/04

NDA 21-675
Zylet (Loteprednol Etabonate 0.5%/Tobramycin 0.3% Suspension: Resub DFS Version Dec 7, 2004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-675	
Brand Name:	Zylet™
Generic Name:	Loteprednol Etabonate and Tobramycin Ophthalmic Suspension, 0.5%/0.3%
Dosage Form:	Ophthalmic Suspension
Dosage Strength:	0.5%/0.3%
Indication:	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
NDA Type:	Type 1 Resubmission
Submission Date(s):	09/10/2004, 10/14/2004, 11/01/2004, 12/02/2004
Sponsor:	Bausch & Lomb, Inc.Rochester, NY
Reviewer:	Chandra S. Chaurasia, Ph.D.
Team Leader:	E. Dennis Bashaw, Pharm. D.
OCPB Division:	DPE III (HFD-880)
OND Division:	DAAODP (HFD-550)

1. BACKGROUND

During the original review of this NDA 21-675, the following comments were noted:

While from clinical perspective, the relevance of loteprednol aqueous humor concentrations at 40- and 60-minute time points is not well understood, the demonstration of penetration into the aqueous humor is considered to be positive. Even so, the pivotal "bioequivalency" trial did not meet the pre-agreed upon "bioequivalency criteria" at these sampling time points. It is also noted that from the Clinical Pharmacology and Biopharmaceutics perspective, the design of the pivotal study 358-006 did not meet the requirements of 21CFR320 in that the data collected is unable to demonstrate the "rate and extent of absorption" as required by the regulations.

In the Approvable letter dated July 7, 2004, the Agency provided the following comments among others:
"Review of the analytical portion of the BLP-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."

In subsequent meetings with the Sponsor on Aug 11 and 12, 2004, the Agency indicated that testing the retained clinical samples at an alternate lab would be a reasonable approach for addressing the above deficiencies.

In the current submission the Sponsor has provided results of data from the remaining samples from pivotal bioequivalence study BLP 358-006. The assay was carried out by an alternative laboratory, [ ] using a validated [ ] method. Two-hundred and thirty clinical samples were analyzed.

The Sponsor's response was reviewed by the Office of Clinical Pharmacy and Biopharmaceutics. The review is described in Appendix 2 of this document. The following comments are based on the review of the resubmitted data.

COMMENTS

The Sponsor's response has basically provided a comparison of the mean and variance of the results for the two treatment groups (Loteprednol [LET] and lotemax [LX]) at two time intervals (40 and 60 minutes) produced by [ ] with the results that [ ] produced previously. The Sponsor has also presented a scatter plot showing a head-to-head comparison of the assays for 105 samples tested at [ ] and where past results were also available from [ ]. The results of this comparison exhibit a correlation coefficient of 0.8. Based on results of this comparison, the Sponsor claims that analysis of the retained clinical samples at [ ] fully corroborates the data generated by [ ] and supports the bioequivalence of LET to LX.

However, the Sponsor has not provided the 90% confidence intervals for the 40- and 60-minute time-points for the data obtained from the 230 samples re-analyzed by the alternative laboratory [ ] It is noted that the correlation of the results form [ ] and [ ] is only 0.8 and also that this shows a linear trend at the lower concentrations only. Furthermore, corroboration of assay results between data from [ ] may be considered a cross method validation at best, and may not be used to establish bioequivalency between the test and reference products. It is emphasized that to establish bioequivalency between loteprednol etabonate component of the test product Zylet™ and reference products Lotemax under the conditions of resubmission of this NDA, statistical analysis must be done comparing the data between the test and reference products obtained only from the samples generated at the alternate laboratory [ ]

RECOMMENDATIONS

Upon reviewing the information submitted in support of the NDA for loteprednol etabonate and tobramycin ophthalmic suspension 0.5%/0.3%, the Office of Clinical Pharmacology and Biopharmaceutics found that the information submitted does not meet the requirements of 21CFR320. From the Clinical Pharmacology and Biopharmaceutics perspectives, the Sponsor has not provided adequate data to establish bioequivalency between loteprednol etabonate component of the test product Zylet™ (loteprednol etabonate 0.5%/tobramycin 0.3%) and reference products Lotemax.

Subsequent to the previous recommendation the sponsor submitted the missing information in a document dated 12/02/2004. The following addendum to the review contains our interpretation and final conclusions regarding this submission.

Addendum to the Review:

At the request of the Medical Officer, Dr. Boyd, a telecom was held on Dec. 1st 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 this review, as it attempted to validate the [ ] laboratory data. In our discussions with the sponsor the FDA has repeatedly emphasized that the [ ] data was not acceptable. We were willing to consider an independent re-analysis of the remaining samples as a standalone assessment of bioavailability but not as a route to validate the [ ] work. During the telecom the sponsor was asked to repeat the statistical analysis for bioequivalency on just the [ ] database. Because of the short timeline involved, the sponsor was asked to fax the results to the FDA and to follow it up with an official submission of the re-analysis as soon as possible.

	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. While it is true that the sponsor still failed to properly analyze the data (in that they constructed 95% confidence intervals instead of 90% confidence intervals), construction of 90% confidence intervals would be of little value given the extreme nature of the calculated interval.

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.

Final 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.

/S/

Chandra S. Chaurasia, Ph.D. _____ Date: _____
Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III, HFD-880

/S/

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____ Date: _____
Team Leader, HFD 880

CC: NDA 21-675, HFD-850 (P. Lee), HFD-550 (R. Rodriguez), HFD-880 (J. Lazor, A. Selen)

2. DETAILED LABELING RECOMMENDATIONS

The labeling comments related to Clinical Pharmacology sections (where appropriate) are provided below. ***Blue underline*** indicates suggested additions, strikethrough-indicates deletions of the labeling contents.

CLINICAL PHARMACOLOGY:
Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent. It is highly lipid soluble which enhances its penetration into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

The antibiotic component in the combination (tobramycin) is included to provide action against susceptible organisms. *In vitro* studies have demonstrated that tobramycin is active against susceptible strains of the following microorganisms:

Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some Streptococcus pneumoniae. Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii, most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius*, *Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species.

Pharmacokinetics:

3. APPENDICES

6 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

NDA 21-675
Zylet (Loteprednol Etabonate 0.5%/Tobramycin 0.3% Suspension: Resub DFS Version Dec 7, 2004

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 [ ] mOsm/kg.

Appears This Way
On Original

3.2. **Appendix 2**

Sponsor's Response

In the current submission the Sponsor has provided results of reanalyzed data of remaining samples from the BLP 358-006 study. The analysis was carried out by an alternative laboratory, [ ] using a validated [ ] method.

Two-hundred and thirty clinical samples were analyzed. The lower limit of detection was [ ] ng/mL. The precision and accuracy of the assay were within the acceptable range of ±15%. The analytical method validation is provided in the NDA resubmission and was found to be acceptable. The results are summarized in the table below.

A comparison of the mean and variance of the results for the two treatment groups Loteprednol (LET) and lotemax (LX) at two time intervals (40 and 60 minutes) produced by — with the results that [ ] produced previously is provided in Tables 1 and 2 below:

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 scatter plot (Figure 1) showing 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. As evident from the graph, there seem to be a trend of linear relationship at the lower concentration only. A linear relationship trend at the higher concentrations may be misleading.

NDA 21-675
Zylet (Loteprednol Etabonate 0.5%/Tobramycin 0.3% Suspension: Resub DFS Version Dec 7, 2004
Following a request from the Agency on Oct 22, 2004, the Sponsor submitted histograms showing the distribution of the newly validated data sets from both [ ] using same scale and same bin size (Figures 2A and 2B). From the frequency distribution, no clear signal of correlation between the two data set could be interpreted.

Comments:
Based on the comparative results between the 105 samples tested both at [ ], the Sponsor states that analysis of the retained clinical samples at an independent laboratory fully corroborates the data generated by [ ] and supports the bioequivalence of LET to LX.

It is noted that the correlation of the results form [ ] is only 0.8 exhibiting a somewhat linear trend. corroboration of analytical results between data from [ ] and this approach may be considered a cross analytical method validation at best, but the bioequivalence between the test and reference products could only be based on data generated from the remaining samples analyzed by the alternate laboratory [ ]

However, the Sponsor has not provided the 90% confidence intervals for the 40- and 60-minute time-points for the data obtained from the 230 samples re-analyzed by the alternative laboratory [ ] It is noted that the correlation of the results form [ ], is only 0.8 and also that this shows a linear trend at the lower concentrations only. Furthermore, corroboration of assay results between data from [ ]. may be considered a cross method validation at best, and may not be used to establish bioequivalency between the test and reference products. It is emphasized that to establish bioequivalency between loteprednol etabonate component of the test product Zylet™ and reference products Lotemax under the conditions of resubmission of this NDA, statistical analysis must be done comparing the data between the test and reference products obtained only from the samples generated at the alternate laboratory [ ]

Figure 1

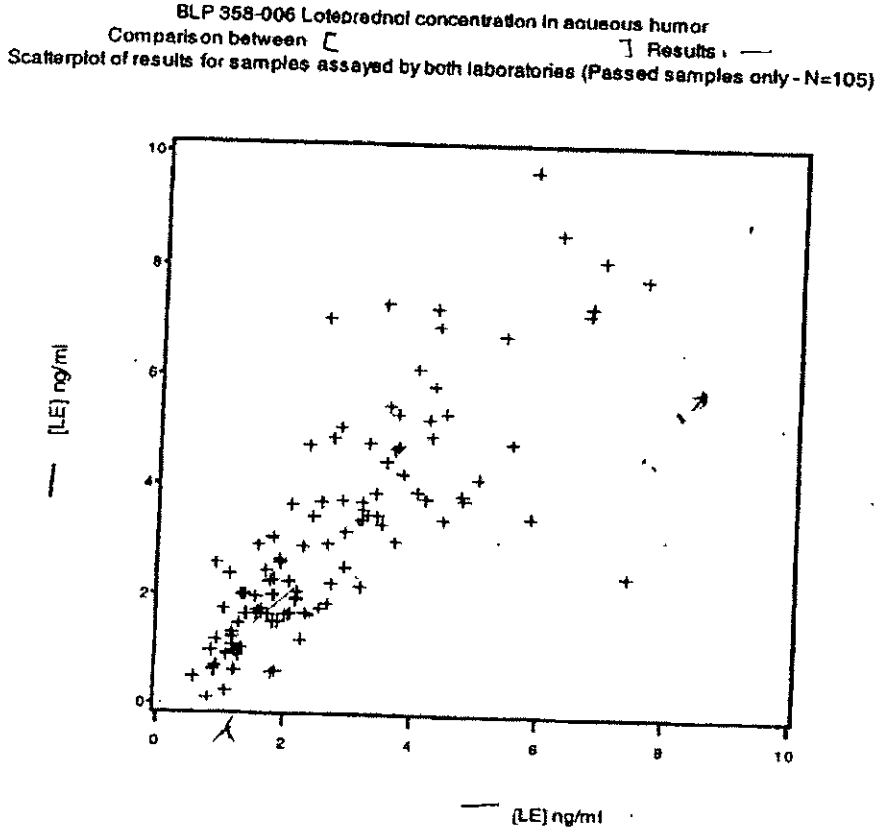
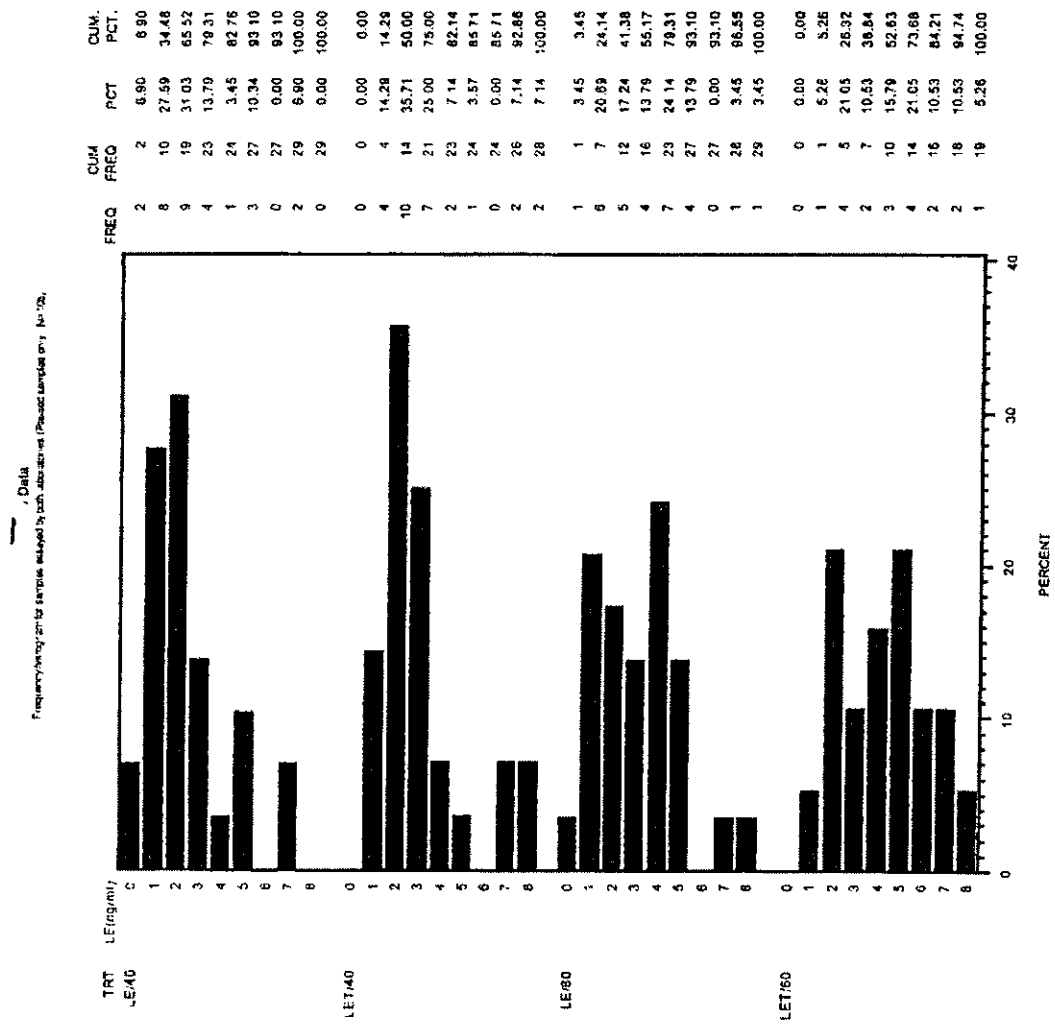
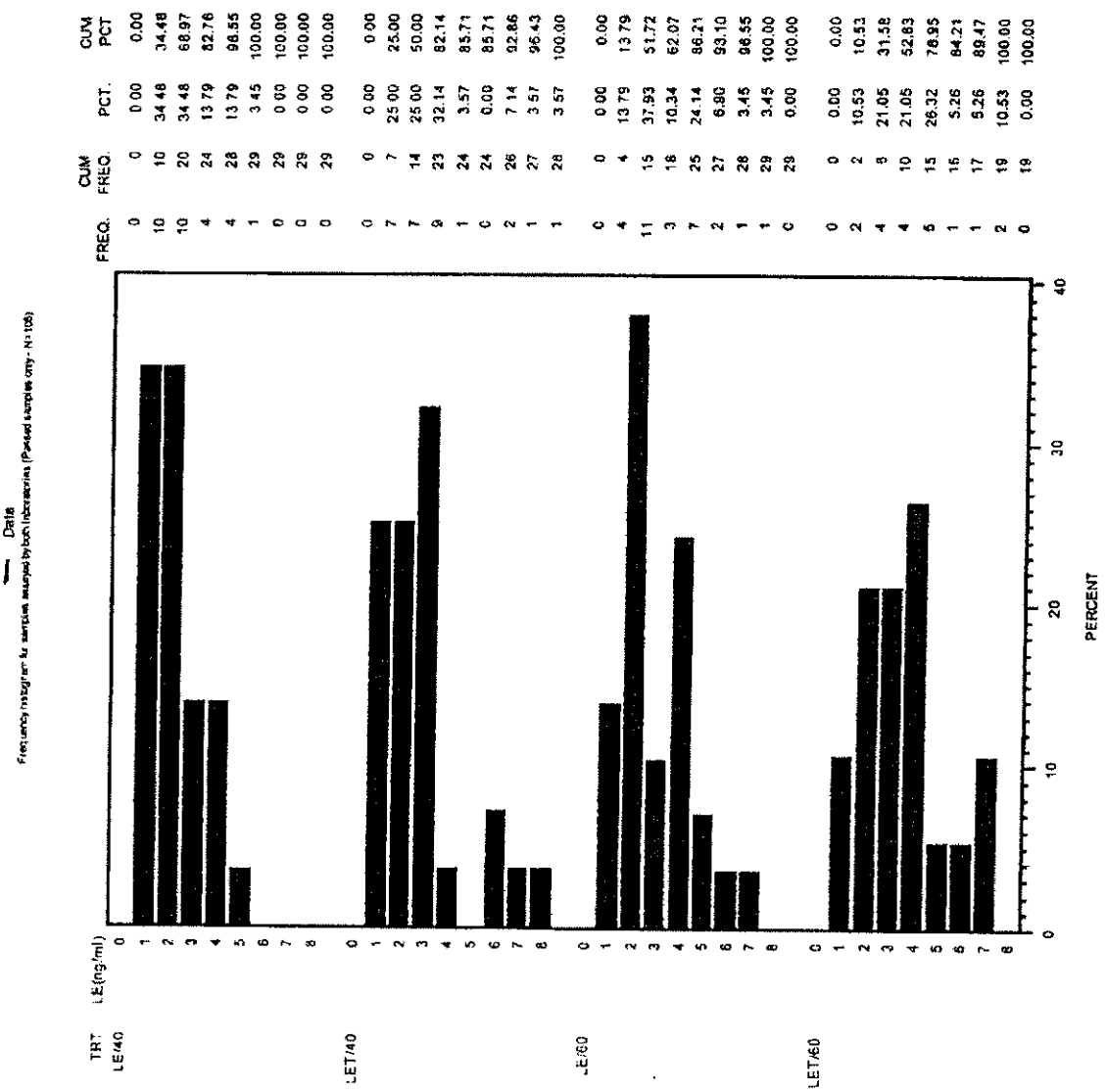

BLP 358-006 Loteprednol concentration in aqueous humor
Comparison between [ ] Results
Scatterplot of results for samples assayed by both laboratories (Passed samples only - N=105)
[LE] ng/ml
[LE] ng/ml
0
2
4
6
8
10

Figure 2 A.


TRT
LE/40
LE/80
LET/40
LET/60
LE(ng/ml)
FREQ
CUM FREQ
PCT
CUM. PCT.
PERCENT
0
10
20
30
40

NDA 21-675
Zylet (Loteprednol Etabonate 0.5%/Tobramycin 0.3% Suspension: Resub DFS Version Dec 7, 2004

Figure 2 B.



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/s/

Chandra S. Chaurasia
12/7/04 03:59:25 PM
BIOPHARMACEUTICS

Dennis Bashaw
12/7/04 04:07:25 PM
BIOPHARMACEUTICS

6/15/04

NDA 21-675
Zylet (Loteprednol Etabonate 0.5%/Tobramycin 0.3% Suspension: DFS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-675

Brand Name:	Zylet™
Generic Name:	Loteprednol Etabonate and Tobramycin Ophthalmic Suspension, 0.5%/0.3%
Dosage Form:	Ophthalmic Suspension
Dosage Strength:	0.5%/0.3%
Indication:	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
NDA Type:	Original NDA
Submission Date(s):	09/08/2003, 04/19/04, 04/22/04
Sponsor:	Bausch & Lomb, Inc.Rochester, NY
Reviewer:	Chandra S. Chaurasia, Ph.D.
Team Leader:	E. Dennis Bashaw, Pharm. D.
OCPB Division:	DPE III (HFD-880)
OND Division:	ODE V (HFD-550)

TABLE OF CONTENS

I. EXECUTIVE SUMMARY

Zylet™ (loteprednol etabonate 0.5% and tobramycin ophthalmic 0.3% suspension) is a topical anti-inflammatory and antibiotic combination product developed by Bausch & Lomb for the treatment of steroid-responsive inflammatory ocular conditions and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. Loteprednol etabonate (LET) is the corticosteroid anti-inflammatory component of the combination product. Tobramycin is the antibiotic component included to provide action against susceptible organisms. This combination

product is not available in the US. A similar combination product containing the steroid dexamethasone 0.1% and tobramycin 0.3% is available for the same indication.

For the purpose of assessing the relative bioavailability of combination products, 21 CFR 320.25(g)(2) allows for the use of currently marketed single-ingredient drug products as reference products (administered in combination). Both loteprednol etabonate in 0.5% strength (NDA 20-583, Lotemax®, Bausch & Lomb) and tobramycin in 0.3% strength (NDA 50-541, Tobrex® , Falcon and ANDA 64-052, Bausch & Lomb) are available in the US as single ingredient products for topical ophthalmic administration. Historically, the safety and efficacy of tobramycin in ophthalmic products have been evaluated by an in vitro microbial kill rate method without a traditional bioavailability assessment. Since, the antibiotic is included for its local effect against superficial bacterial ocular infection, the "bioavailability" of the tobramycin component is not considered a relevant issue. The adequacy of the in vitro microbial kill rate study was evaluated by both the Medical and Microbiology reviewers and will not be covered in this review.

Bausch and Lomb has submitted this NDA as a 505(b)(2) application. In support of the NDA submission, the sponsor has submitted five clinical studies and one microbial kill rate study. Two of the 5 clinical studies, protocol 358-005 and 358-006 are pilot and pivotal clinical pharmacology studies, respectively. These studies are subject to review by the Clinical Pharmacology and Biopharmaceutics Division. Three other clinical studies, 358-002, 358-003 include safety and 358-004 include clinical equivalence studies.

The approvability of this application (as submitted) rests upon the results of the pivotal in vivo biopharmaceutics trial. The other three clinical studies were either powered to demonstrate safety and tolerability of the combination product or failed to show therapeutic equivalence between the combination product and the single entity products, used in combination. These in vivo clinical trials used a conjunctival provocation test based on endpoints determined by the Ophthalmologic Review Team. They have been evaluated for safety and represent the safety database for this NDA.

Protocol BLP 358-006

To support the human pharmacology and bioavailability of the steroidal component, the sponsor has provided results of "bioequivalence" study (protocol BLP 358-006) comparing loteprednol etabonate to the RLD Lotemax®. This "bioequivalence" study was conducted in male and female patients undergoing routine cataract surgery. Aqueous humor concentrations of loteprednol etabonate at two time points 40- and 60-mintues were compared following topical administration of 4 drops of the test and reference products over a period of 10 minutes.

As noted above, the design of the pivotal "bioequivalence" study 358-006 includes only two sampling points at 40 and 60 min for all subjects. (*The smaller pilot study 358-005 used 20 and 40 minute sampling points.*) This approach to establishing "bioequivalence" is directly at odds with the standard methods of pharmacokinetics which use sampling at several relevant time points to determine the rate (Cmax) and extent of absorption (AUC). The trial itself was designed by the Ophthalmologic Review team without the input of the Division of Pharmaceutical Evaluation-III back in the early 1990's (please see attachment in Appendix in Section 4.3: Memo to File from Dr. Veneeta Tandon and Dr. Dennis Bashaw, Office of Clinical Pharmacology and Biopharmaceutics, IND 36,209/N034, 07/23/02).

As part of the study design, the Clinical Division recommended using a 95% confidence interval approach to establish bioequivalency at both 40- and 60-minutes time point. A 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."*

Analytical Results
It is further noted that 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-minue time point remained outside this range.

Study Results
These results are only being included here for completeness sake as they have no pharmacokinetic validity in themselves as to establishing the "rate and extent of absorption" as required under 21CFR320. 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 failed to demonstrate "bioequivalence" at the 40-min time point per the a priori criterion recommended by the Clinical Division.

Conclusion
While from clinical perspective, the relevance of loteprednol aqueous humor concentrations at 40- and 60-minute time points is not well understood, the demonstration of penetration into the aqueous humor is considered to be positive. Even so, the pivotal "bioequivalency" trial did not meet the pre-agreed upon "bioequivalency criteria" at these sampling time points. It is also noted that from the Clinical Pharmacology and Biopharmaceutics perspective, the design of the pivotal study 358-006 did not meet the requirements of 21CFR320 in that the data collected is unable to demonstrate the "rate and extent of absorption" as required by the regulations.

NDA 21-675
Zylet (Loteprednol Etabonate 0.5%/Tobramycin 0.3% Suspension: DFS

Recommendations: The loteprednol etabonate component of the test product Zylet™ (loteprednol etabonate 0.5%/tobramycin 0.3%) did not meet the pre-agreed on "bioequivalency criterion", i.e., 95% confidence intervals between 80-125% at both the 40- and 60-minute time points. Upon reviewing the information submitted in support of the NDA for loteprednol etabonate and tobramycin ophthalmic suspension 0.5%/0.3%, the Office of Clinical Pharmacology and Biopharmaceutics found that the information submitted does not meet the requirements of 21CFR320.

Phase IV Commitment: Not recommended at this point.

Summary of Important Clinical Pharmacology and Biopharmaceutics Findings
Bioequivalence Studies:
The NDA 21-675 is a 505 (b)(2) application. In support of this application the sponsor submitted a "bioequivalence" study (BPL 58-006) to establish the bioequivalency of loteprednol etabonate in the test product to the RLD Lotemax. The pivotal BE study included comparison of loteprednol etabonate, 0.5% in the combination test product with the RLD Lotemax® (Lotemax etabonate, 0.5%). The 95% confidence intervals for the 40- and 60-minute time point post dosage administrations were obtained per a priori recommendations from the Clinical Division. The comparative mean aqueous humor concentrations and statistical results for loteprednol are provided in the Tables below:

Table 1. Loteprednol concentration (ng/mL) by treatment group in primary evaluable patients

	40 min Treatment		60 min Treatment	
	Lotemax	LET	Lotemax	LET
N	348	346	365	360
Mean	2.433	2.810	3.818	4.078
SD	2.103	2.491	2.341	2.158
Median	1.905	2.300	3.300	3.680
Min	[redacted]			
Max	[redacted]			

Table 2. Loteprednol concentration log transformed mean and 95% confidence intervals for primary evaluable patients.

Time	Treatments	Mean	SEM	Ratio: LET/Lotemax	95% CI	
					Lower	Upper
40 min	LET	2.101	0.04337	1.16	77.7	95.5
	Lotemax	1.810	0.04344			
60 min	LET	3.473	0.04270	1.11	81.5	99.7
	Lotemax	3.129	0.04254			

Based on the DSI comments in Form-483, Bausch & Lomb performed a re-analysis of the bioequivalence study data excluding runs 7,10,13,17, 24,27,30,45 and 54. These results are summarized in the Table below:

NDA 21-675
Zylet (Loteprednol Etabonate 0.5%/Tobramycin 0.3% Suspension: DFS

Table 3: Study BLP 358-006 Bioequivalence Analysis Excluding Samples from Analytical Runs #7,10,13,17, 24,27,30,45 and 54 Per [ ] Form FDA 483 Observations. LE Concentration (In ng/mL)

Time	Treatment	Mean	SEM	Lower	Upper	95% CI
40 min	LET	0.6995	0.0460	0.6086	0.7903	76.6-96.4%
	Lotemax	0.5474	0.0453	0.4580	0.6369	
	LX/LET	-0.1520	0.0582	-0.2670	-0.0371	
60 min	LET	1.2027	0.0447	1.1144	1.2910	82.1-102.9%
	Lotemax	1.1189	0.0444	1.0311	1.2067	
	LX/LET	-0.0838	0.0571	-0.1967	0.0291	

Mean is as estimated by ANOVA methods.
Confidence Intervals (Upper and Lower) at 95.162% (alpha = 0.0484).

As reported in Table 2, the 95 % confidence interval for Cmax at 40 min sampling time was in the range of 77.7-95.5%, and was outside the range of 80-125%. However, the corresponding value at 60 minute sampling time (81.5-99.7%) was within this range. Similar results were obtained upon re-analysis of data excluding runs 7,10,13,17, 24,27,30,45 and 54 based on the DSI recommendations – the 95% confidence intervals for the 60 min sampling was within the range of 80-125% but that for the 40 min sampling was outside this range (Table 3 above).

/S/

Chandra S. Chaurasia, Ph.D. _____ Date: _____
Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III

/S/

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____ Date: _____

CC: NDA 21-675, HFD-850 (P. Lee), HFD-550 (R. Rodriguez), HFD-880 (J. Lazor, A. Selen)

NDA 21-675
Zylet (Loteprednol Etabonate 0.5%/Tobramycin 0.3% Suspension: DFS

Question Based Review

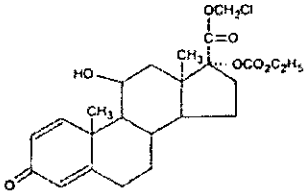
2.1 General Attributes of Loteprednol/Tobramycin

2.1.1 What regulatory background or history information contribute to the assessment of the clinical pharmacology and biopharmaceutics of this drug?

Bausch and Lomb has submitted this NDA as a 505(b)(2) application. To support the human pharmacology and bioavailability, the sponsor has provided results of "bioequivalence" study (protocol BLP 358-006) comparing loteprednol etabonate to the RLD Lotemax®. The BE study was conducted in male and female patients undergoing routine cataract surgery. The aqueous humor concentrations of loteprednol etabonate at two time points 40- and 60-mintues were compared per recommendations by the Clinical Division (please also see Appendix in section IV Memo to File by Drs. Veneeta Tandon and Dennis Bashaw with regards to OCPB's position on establishing bioequivalence using the two 40-and 60-min time points). Historically, the safety and efficacy of tobramycin in ophthalmic products have been evaluated by an in vitro microbial kill rate method without a traditional bioavailability assessment. Since, the antibiotic is included for its local effect against superficial bacterial ocular infection, the "bioavailability" of the tobramycin component is not considered a relevant issue. The adequacy of the in vitro microbial kill rate study was evaluated by both the Medical and Microbiology reviewers and will not be covered in this review.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the product?

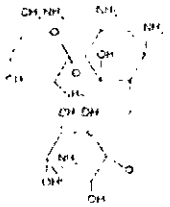
Structural formula Loteprednol etabonate:



$C_{24}H_{31}ClO_7$ Mol. Wt. 466.96

Chemical name: chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate

Structural formula Tobramycin:



$C_{18}H_{37}N_5O_9$ Mol. Wt. 467.52

Chemical Name: *O*-3-Amino-3-deoxy- α -D-glucopyranosyl-(1 → 4)-*O*- [2,6-diamino-2,3,6-trideoxy- α -D-*ribo*-hexopyranosyl- (1→ 6)] -2-deoxystreptamine

Each mL contains: Actives: Loteprednol Etabonate 5 mg (0.5%) and Tobramycin

3 mg (0.3%).Inactives: Edetate Disodium, Glycerin, Povidone, Purified Water and Tyloxapol. 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 [redacted] mOsm/kg.
Preservative Added: Benzalkonium Chloride 0.01%

2.1.3. What are the proposed mechanism of action and therapeutic indication of loteprednol 0.5%/tobramycin 0.3%?

Mechanism of Action:
There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid.

The antibiotic component in the combination (tobramycin) is included to provide action against susceptible organisms.

Indication: 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

2.1.4 What is the proposed dosage and route of administration?

The proposed dose is one or two drops of Zylet into the conjunctival sac of the affected eye(s) every four to six hours. During the initial 24 to 48 hours, the dosing may be increased, to every one (1) to two (2) hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely

2.2. General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To support the human pharmacology and bioavailability of this NDA, the sponsor has provided results of a phase 3 "bioequivalence" study (protocol BLP 358-006) comparing loteprednol etabonate (in the combination product) to the RLD Lotemax®. The BE study was conducted in 2,788 male and female patients undergoing routine cataract surgery. The aqueous humor concentrations of loteprednol etabonate at two time points 40- and 60-mintues were compared following topical administration of 4 drops of the test and reference products over a period of 10 minutes (please refer to Memo to File by Drs. Veneeta Tandon and Dennis Bashaw, Appendix Section IV of this review). As mentioned above, the safety and efficacy of the tobramycin component was evaluated by an in vitro "microbial kill curve" method without a traditional bioavailability assessment.

In additions the Sponsor also conducted a pilot phase 2 bioequivalence studies BLP 358.005 comparing the aqueous humor concentration of Loteprednol Etabonate following administration of Bausch & Lomb Pharmaceuticals, Inc. Loteprednol Etabonate and Tobramycin Ophthalmic Suspension, 0.5%/0.3% (LET) or Lotemax (Loteprednol Etabonate Ophthalmic Suspension, 0.5%) in patients during routine cataract surgery in 68 males and females undergoing routine

cataract surgery. The aqueous humor concentrations of loteprednol etabonate at two time points 20- and 40-mintues were compared following topical administration of 2 drops of the test and reference products over a period of 10 minutes.

2.2.2 What is basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

No new information has been submitted for the current combination product as the respective concentrations of the loteprednol etabonate and tobramycin in the NDA 21-675 combination product are the same as that approved for single agent loteprednol etabonate, 0.5% suspension, Lotemax® or tobramycin, 0.3% solution, Tobrex®.

2.2.3 Are the active moiety in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The Sponsor measured the loteprednol etabonate in aqueous humor in the BE study. See Analytical section Appendix 4.2 (page 20) for more details.

2.2.4. Exposure-response evaluations

No new information has been submitted for the current combination product as the respective concentrations of the loteprednol etabonate and tobramycin in the NDA 21-675 combination product are the same as that approved for single agent loteprednol etabonate, 0.5% suspension (NDA 20-583, Lotemax®, Bausch & Lomb) or tobramycin, 0.3% solution Lotemax® or tobramycin, 0.3% solution, Tobrex®.

2.2.5. What are the pharmacokinetic characteristics of the drug and its metabolite?

The combination product is topically used as ophthalmic suspension dosage form, and has no noticeable systemic absorption at the limit of detection of — g/mL. The current NDA is based on establishing "bioequivalence" between loteprednol etabonate in the proposed test product with the RLD Lotemax in aqueous humor. It is also noted that historically, the safety and efficacy of tobramycin in ophthalmic products have been evaluated by an in vitro microbial kill rate method without a traditional bioavailability assessment.

2.3. Intrinsic Factors

No new information has been submitted for the current combination product. The sponsor's proposed labeling include Class Labeling that for Lotemax and Tobrex.

2.4. Extrinsic factors

No new information has been submitted for the current combination product. The sponsor's proposed labeling include Class Labeling that for Lotemax and Tobrex.

2.5 General Biopharmaceutics

2.5.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility and permeability data support this classification?

The product in this NDA is a topical suspension for ophthalmic administration.

2.5.2. What is composition of the to-be-marketed formulation?

The component and compositions of the test and reference products are given below:

Ingredients (per mL)	**Lotemax**	**LET**
Loteprednol etabonate 0.5% (5 mg)	0.05%	0.05%
Glycerin		
Povidone,		
Povidone,		
Tobramycin		0.3%
Benzalkonium chloride		
Tyloxapol		
Edetate disodium		
Purified water		
Sulfuric acid or sodium hydroxide	qs to adjust pH	qs to adjust pH

2.5.3 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

Formulations of the BE batch and proposed to-be-marketed product are same.

2.5.4 What moieties should be assessed in bioequivalence studies?

The parent drug loteprednol etabonate. It is also noted that per the current Agency practice, the safety and efficacy of tobramycin in ophthalmic products are evaluated by an in vitro microbial kill rate method without a traditional bioavailability assessment.

2.6 Analytical Section

2.6.1 Were relevant metabolite concentration measured in the clinical pharmacology and biopharmaceutics studies?

The applicant measured the active moiety loteprednol etabonate in all the BE studies.

2.6.2 For all moieties measured, was free, bound, or total measured? What is the basis of that decision, and is it appropriate?

No new information has been submitted for the current combination product as the respective concentrations of the loteprednol etabonate and tobramycin in the NDA 21-675 combination product are the same as that approved for single agent loteprednol etabonate, 0.5% suspension (NDA 20-583, Lotemax®, Bausch & Lomb) or tobramycin, 0.3% solution Lotemax® or tobramycin, 0.3% solution, Tobrex®.

2.6.3 Were the analytical procedures used to determine drug concentration in this NDA acceptable?

No. Please see the Analytical Determinations/Drug Concentration Measurements Appendix Section 4.2 Clinical Pharmacology and Biopharmaceutics Individual Study Review for Protocol BLP 358/006.

3. Labeling Recommendations

No recommendations are made at this time.

4. Appendices

4.1 Proposed Package Insert (Original and Annotated)

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9 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

4.2. Clinical Pharmacology and Biopharmaceutics Individual Study Review

Protocol BLP 358-006: A phase 3, randomized, double-masked, multi-center comparison of the aqueous humor concentration of Loteprednol Etabonate, at two time points 40 and 60 minutes following administration of Bausch & Lomb Loteprednol Etabonate and Tobramycin Ophthalmic Suspension, 0.5%/0.3% (LET) or Lotemax (Loteprednol Etabonate Ophthalmic Suspension, 0.5%) in patients undergoing routine cataract surgery, N=2788.
Study Center/Investigator: The study was conducted at 26 centers in the US. The principal investigators and names of the centers are given on page 007, Vol. 2.06. The study samples were analyzed at [redacted]
Study Subjects: Two thousand seven hundred and eighty-eight subjects, males and females, ≥18 years old in the study scheduled for primary cataract extraction, with visual acuity of at least 20/200 were enrolled in the study. The mean age group was 71.5 years. Females comprised 59% of the study population. The majority of subjects were white (87%, 2415/2788). Detail of the demographic is provided on page 042, Vol 2.06 of the submission. Two thousand subjects completed the study. Inclusion and exclusion criteria are described on pages 25-26, Vol. 2.06.
Treatment: The subjects received 4 droplets of LET or Lotemax over a period of 10 minutes at a nominal 40 or 60 minutes prior to aqueous humor extraction. All medications were instilled by the study personnel. There were four treatment groups in this study:
Lotemax dosed and aqueous humor sampled 40 min after the last instillation.
Lotemax dosed and aqueous humor sampled 60 min after last instillation.
LET dosed and aqueous humor sampled 40 min after the last instillation.
LET dosed and aqueous humor sampled 60 min after last instillation.
Study Dates: Clinical study was performed between 10/05/2001 to 12/11/2002.
Drug Formulations: Test: Loteprednol Etabonate/Tobramycin 0.5%/0/3% Ophthalmic Suspension, Lot 395331). **Reference**: Lotemax (loteprednol etabonate) 0.3%, Lot 336342.
Sampling: Aqueous humor aliquots collected within ± 5 minutes of the schedules time after receiving the last dose of study medication. Each sample (100-125 µL) was obtained from the anterior chamber though the surgical incision. The details of the sample collection are described in Volume 2.01, page 131.
Analytical Determinations/Drug Concentration Measurements
The loteprednol concentrations were measured using a validated [redacted] method with a limit of detection of [redacted] ng/ml.
Analytical method validation used for the study samples is provided under report [redacted]-017-06 (Vol. 2.34, page 123). It is noted that the firm has used a broader acceptance criteria for the calibration and QC sample runs than those recommended in the Agency's Guidance for Industry: Analytical Method Validation, May 2001. This was also noted by the Division of Scientific Investigation during the inspection of the [redacted] analytical facility (please see Appendix Section IV of this review DSI report and Form 483 issued to [redacted] The firm's response to Form-483 and this reviewer's comments are summarized on page 22 below. The standard curve range was from [redacted] ng/mL. The accuracy value ranged from [redacted] ng/mL to [redacted] at [redacted] ng/mL. The precision ranged from [redacted] ng/mL. The co-relation coefficient of the calibration runs was [redacted] Inter day accuracy for the QC samples ([redacted]) were reported as [redacted] %, respectively. The corresponding values for precision were [redacted] respectively. Long-term stability was demonstrated for 45 days at -20 ± 5 °C and 93 days at -80 ± 10 °C.

Of the 2788 subjects, 4 did not receive any treatment. No usable aqueous humor could be collected for 89 subjects, and additional 665 subjects had no assay data available due to analysis failures. Thus, assay results were available from 2,030 subjects. Of the 2,030 passed samples, 2.8% (57/2030, 44 in the 40 min dosing and 13 in the 60 min dosing groups) were below the LOQ (— ng/mL).

As reported by the firm the analytical laboratory initially conducted a 45 day aqueous humor samples stability study. Since some of the clinical samples were not assayed within the 45 days of collection, a long term stability study was subsequently conducted that included three time points 60 days, 75 days and 91 days. The firm states that based on the Agency's recommendation only — days stability population bioequivalence data are presented.

Samples from 96 subjects were not supported by the — stability data and were not included in the bioavailability analysis.

Pharmacokinet Results:
There were 1,419 subjects for primary evaluation who met requirements consistent with inclusion/exclusion criteria. Results from these subjects are presented in the bioavailability evaluations.

The mean loteprednol etabonate concentrations is given in Table 1 below. The natural log values of the respective data and the 95% confidence interval are provided in Tables 2 and 3, respectively.

Table 1.Loteprednol concentration (ng/mL) by treatment group in primary evaluable patients

	40 min Treatment		60 min Treatment	
	Lotemax	LET	Lotemax	LET
N	348	346	365	360
Mean	2.433	2.810	3.818	4.078
SD	2.103	2.491	2.341	2.158
Median	1.905	2.300	3.300	3.680
Min				
Max				

Table 2.Loteprednol concentration (loge ng/mL) by treatment group in primary evaluable patients

	40 min Treatment		60 min Treatment	
	Lotemax	LET	Lotemax	LET
N	348	346	365	360
Mean	0.601	0.761	1.0149	1.240
SD	0792	0.772	0.653	0.641
Median	0.644	0.833	1.194	1.303
Min				
Max				

Table 3. Loteprednol concentration log transformed mean and 95% confidence intervals for primary evaluable patients.

Time	Treatments	Mean	SEM	Ratio: LET/Lotemax	95% CI	
					Lower	Upper
40 min	LET	2.101	0.04337	1.16	77.7	95.5
	Lotemax	1.810	0.04344			
60 min	LET	3.473	0.04270	1.11	81.5	99.7
	Lotemax	3.129	0.04254			

Form-483 and Division of Scientific Investigation Recommendations:
Dr. Nilufer M. Tampal from the Agency's Division of Scientific Investigation (HFD-48) conducted an inspection of the [ ] analytical facility on 3/29-4/02/04. Based on the inspection results, the DSI issued Form 483 (see attachment) and made the following recommendations:

1. All subjects loteprednol (LE) concentrations from Runs 7, 10, 24, 30, 45, and 54 (item #1 and 2) be excluded from BE determinations.
2. Data from Study [ ]-017-06 (Bausch & Lomb Study BLP 358-006) not be accepted for agency review until long term stability, freeze/thaw stability [ ] and stock solution stability of LE have been demonstrated (item #3).
3. In order to apply consistent standards across the industry, in absence of any justifiable data, the use of broad acceptance limits for the analytical method using a [ ] assay should not be permitted (item #5).

Review of Bausch & Lomb/ [ ] Response to Form-483
On April 16, and April 21, 2004, [ ] and Bausch & Lomb responded to the Agency's concerns raised in Form 483 (please see attached for details), respectively.

Based on the DSI recommendations, Bausch & Lomb performed a re-analysis of the bioequivalence study data excluding runs 7,10,24,30,45 and 54. These results are summarized in the Table 4 below:

Table 4: Study BLP 358-006 Bioequivalence Analysis Excluding Samples from Analytical Runs #7,10,13,17, 24,27,30,45 and 54 Per [ ] Form FDA 483 Observations. LE Concentration (In ng/mL)

Time	Treatment	Mean	SEM	Lower	Upper	95% CI
40 min	LET	0.6995	0.0460	0.6086	0.7903	76.6-96.4%
	Lotemax	0.5474	0.0453	0.4580	0.6369	
	LX/LET	-0.1520	0.0582	-0.2670	-0.0371	
60 min	LET	1.2027	0.0447	1.1144	1.2910	82.1-102.9
	Lotemax	1.1189	0.0444	1.0311	1.2067	
	LX/LET	-0.0838	0.0571	-0.1967	0.0291	

Mean is as estimated by ANOVA methods.
Confidence Intervals (Upper and Lower) at 95.162% (alpha = 0.0484).

With respect to DSI recommendation #2 above (item #3 in Form-483), in a letter to the Agency dated April 16, 2004 the analytical laboratory [ ] acknowledged the Agency's concern and has made commitment of submitting appropriate documentation on bench top, freeze/thaw, stock solution and long term stability by May 28, 2004.

With respect to DSI recommendation #3 above (item #5 in Form-483), [ ] states that the broader range for calibration standard is in compliance with the provisions in the FDA Guidance for Industry Bioanalytical Method Validation, May 2001. The firm's response is acceptable.

Adverse Events: In this study, the study medication was given pre-operatively. Within 30-days following surgery, two-thirds of the study population experienced adverse events (66.5%, 1852/2784), similarly distributed between the test and reference drugs (66.5%, 926/1396 and 66.7%, 926/1388, respectively). Of these subjects, only in a small proportion, were the AEs judged related to treatment (4.1%, 114/2784). Most of the AEs were mild in severity. Only, a small portion of subjects experienced a serious adverse event (2.3%, 63/2784). Two subjects, one from each treatment group, withdrew from the study due to adverse event. The adverse events are described in detail in section 12.2 Volume 2.06, pp 055.

Comments on bioequivalence study results:
As reported in Table 4, the 95 % confidence interval for Cmax at 40 min sampling time was 77.7% and was outside the range of 80-125%. However, the corresponding value at 60 minute sampling time was within this range. Similar results were obtained upon re-analysis of data excluding runs 7,10,13,17, 24,27,30,45 and 54 based on the DSI recommendations – the 95% confidence intervals for the 60 min sampling was within the range of 80-125% but that for the 40 min sampling was outside this range.

It is noted that the mean values for loteprednol at both time points were slightly higher for the test formulation than that for the reference formulation (point ratios: test/ref 1.16 at 40 min and 1.11 at 60 min dosing groups) indicating that the bioavailability of the test product did not decrease in the presence of tobramycin.

Please also note the firm has submitted data using intent-to-treat population. Based on the results of this analysis, the two treatments were bioequivalent at both the 40 in and 60 min sampling time in the ITT population. However, these data were not reviewed by this reviewer.

In compliance to the DSI's comments in Form 483, [ ] has communicated to the Agency dated April 16, 2004 to address the deficiencies noted by the DSI in the analytical method validation procedures used in the BE study. In light of this, the results of the BE study at 60-min time point may be considered acceptable pending submission and review of the analytical method validation report.

Conclusion on "Bioequivalence" Study:
The design of the "bioequivalence" study in studies 358-005 (pilot) and 358-006 (pivotal) include only two sampling points at 20 and 40 min (358-005), and 40 and 60 min (358-006), respectively for all subjects unlike sampling at several relevant time points in a typical

bioequivalence study design. Considering the complexity involved in sampling the aqueous humor at several time points in each subject, a sparse sampling approach over the range of therapeutically relevant time span would have been a better approach. It is noted that during the development phase of the current NDA, the Clinical Division has recommended to establish bioequivalency at both 40- and 60-minutes time point using a 95% confidence interval approach. (please see attachment in Appendix in Section 4.3: Memo to File from Dr. Veneeta Tandon and Dr. Dennis Bashaw, Office of Clinical Pharmacology and Biopharmaceutics, IND 36,209/N034, 07/23/02).

From the Clinical Pharmacology and Biopharmaceutics perspective, the design of the pivotal study 358-006 using only two time point samplings at 40- and 60-minutes and establishing bioequivalency based on 95% confidence interval is not appropriate. The loteprednol etabonate component of the test product Zylet™ (loteprednol etabonate 0.5%/tobramycin 0.3%) did not meet the pre-agreed on "bioequivalency criterion" recommended by the Clinical Division, i.e., 95% confidence intervals between 80-125% at both the 40- and 60-minute time points.

Protocol BLP 358-005: Pilot aqueous bioavailability study. A pilot phase 2, randomized, single-center comparison of the aqueous humor concentration of Loteprednol Etabonate following administration of Bausch & Lomb Pharmaceuticals, Inc. Loteprednol Etabonate and Tobramycin Ophthalmic Suspension, 0.5%/0.3% (LET) or Lotemax (Loteprednol Etabonate Ophthalmic Suspension, 0.5%) in patients during routine cataract surgery.

Study Center/Investigators: The study was planned as a 2 centers in the US. [redacted] Dr. — began the study, however, his site discontinued after enrolling two subjects.

Analytical Site: [redacted]
Contact Person: [redacted]

Study Subjects: Sixty-eight subjects, males and females, ≥18 years old in the study scheduled for primary cataract extraction, with visual acuity of at least 20/200 were enrolled in the study. The mean age group was 70.3 years. Females comprised 47% (32/68) and males 73 (36/68) of the study population. The majority of subjects were Caucasian (94%, 64/68). Detail of the demographic is provided on page 31, Vol 2.05 of the submission. Of the 68 subjects, 5 received only routine peri-operative medication but no study treatment. Thus, 63 subjects received treatments as given below. Inclusion and exclusion criteria are described on pages 20-21, Vol. 2.05.

Treatment: There were 6 treatment groups in this study. Four groups received 2 drops of study medication. As only one eye was scheduled for cataract surgery, only one eye was dosed:
Lotemax dosed and aqueous humor sampled 20 min after the last instillation (LE/20), N=11.
Lotemax dosed and aqueous humor sampled 40 min after last instillation (LE/40A) N=10.
LET dosed and aqueous humor sampled 20 min after the last instillation (LET/20) N=10.
LET dosed and aqueous humor sampled 40 min after last instillation (LET/40) N=11.

A fifth group received 4 drops of Lotemax and has aqueous humor sampled 20 min after the last instillation (LE/40B) N=21.
A sixth group received no study medication, their aqueous humor serving as blanks N=5.

Subjects 100/001 (LET/40) and 100/002 (LE/20) at [redacted] site were disqualified for receiving local anesthetic within an unacceptable period prior to the collection of aqueous humor (Vo. 2.05, pp. 30).

Study Dates: Clinical study was performed between 09/25/2000 to 03/15/2001.

Drug Formulations: Test: Loteprednol Etabonate/Tobramycin 0.5%/0/3% Ophthalmic Suspension, Lot 165142). **Reference**: Lotemax (loteprednol etabonate) 0.3%, Lot 125402 and 276262.

Sampling: Aqueous humor aliquots collected within ± 5 minutes of the schedules time after receiving the last dose of study medication. Each sample (100-125 µL) was obtained from the anterior chamber though the surgical incision. The details of the sample collection are described in Volume 2.01, page 131.

Analytical Determinations/Drug Concentration Measurements

Analytical Method: Loteprednol etabonate and its metabolite PJ-91 in aqueous humor samples were measured with a validated analytical method [redacted]
The LLOQ for both analytes was [redacted] ng/mL. The mean of the % deviation for calibration curve (range [redacted], was 7.0% (ranged from [redacted]

Handling of dropout or missing data are described in Vol. 2.05, page 34. Of the 63 aqueous humor samples in the 5 active groups, LE concentration in the aqueous humor, 32 were assayed as BLQ, one was above upper limit of quantitation, and 2 were not analyzed due to disqualification. The 32 BLQ observations were analyzed in two ways: as missing or as [redacted] of the LOQ (i.e., [redacted] ng/mL).

Comments on Analytical Method:
Acceptance criteria for the analytical runs are described in Vol 2.05, page 214. These are less rigorous that those in the Agency's Analytical Guidance. For example, the firm's criteria states, "*the mean value of the calibration standards must be within 25% of the actual value except at the LLOQ where it should not deviate by more than 35%*"
Although, the analytical method validation did not meet the current Agency's standard, the results from the analytical runs were considered due mainly to the fact that study BLP358-005 is a pilot study.

Pharmacokinet Results:
LE concentrations by treatment group are provided in the Tables below:
Values of BLQ treated as missing

Measure	LE/20	LE/40A	LET/20	LET/40	LET/40B
N	2	4	2	5	14
Missing	9	6	8	6	7
Mean	0.74	0.76	0.89	1.14	2.36
SD	0.23	0.12	0.21	0.68	2.05
Median	0.74	0.72	0.89	0.92	1.34
Minimum					
Maximum					

Values of BLQ treated as — ng/mL (— of lower LOQ)

Measure	LE/20	LE/40A	LET/20	LET/40	LET/40B
N	10	10	10	10	21
Missing	1	0	0	1	1
Mean	0.35	0.45	0.38	0.70	1.72
SD	0.22	0.27	0.28	0.66	1.96
Median	0.25	0.25	0.25	0.46	0.82
Minimum					
Maximum					

Using the analysis of BLQ as missing, the Lotemax and LET groups sampled at 20 min after the last of two instillations (LE/20 and LET/20, respectively) resulted in similar mean aqueous humor concentration of loteprednol, 0.74 and 0.89 ng/mL, respectively. Similarly, the LE and LET groups sampled 40 minutes after last two instillations (LE/40 and LET/40, respectively) resulted in similar mean aqueous humor concentration for loteprednol, 0.7 and 1.14 ng/mL, respectively. A similar relation was observed between the LE/20 and LET/20 and LE/40 and LET40 sampling groups when analysis was computed using BLQ as — ng/mL (Table 6).
Adverse Events: No adverse event either ocular or systemic were reported in this pilot study. Volume 2.01, pp 170.
Comments on bioavailability:
The objective of this pilot study was to evaluate the bioavailability of loteprednol etabonate and tobramycin ophthalmic suspension, 0.5%/0.3% (LET) compared to Lotemax (loteprednol etabonate suspension 0.5%) at 20- and 40-min time points following topical ophthalmic administration. Measurable aqueous humor concentration of loteprednol etabonate was obtained in 44% (27/61) of eyes at 20 or 40 minutes after last instillation in two sets of direct comparison of Lotemax and LET. Additionally, absorption of loteprednol from Lotemax and LET were comparable at these two time point samplings.

Conclusion on pilot bioavailability study:
In the pilot study, loteprednol concentrations were measurable in 44% (27/61) of eyes receiving two or four drops of Lotemax or LET and sampled 20 or 40 minutes after the last instillation.

4.3. Consult Review (including Pharmacometric Review):
4.3.1. DSI Report and Form 483.

19 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

NDA 21-675
Zylet (Loteprednol Etabonate 0.5%/Tobramycin 0.3% Suspension: DFS

4.4. Cover Sheet and OCPB Filing Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA Number	21-675	Brand Name	Zylet (Proposed)
OCPB Division (I, II, III)	DPE III, HFD 880	Generic Name	Loteprednol Etabonate and Tobramycin Ophthalmic Suspension, 0.5%/0.3%
Medical Division	ODE V, HFD 550	Drug Class	Topical Corticosteroid and aminoglycoside antibiotic combination product
OCPB Reviewer	Chandra S. Chaurasia, Ph. D.	Indication(s)	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.
OCPB Team Leader	E. Dennis Bashaw, Pharm. D.	Dosage Form	Ophthalmic Suspension
		Dosing Regimen	1 or 2 drops into the affected eye q4-6h. During the initial 24 to 48 hours, the dosing may be increased to every 1-2 hours.
Related NDAs/ANDAs	NDA 20-583 Lotemax NDA 20-803 Alrex Alcon's NDA 50-541 Tobrex ANDA 64-052		
Date of Submission	Sep 08, 2003	Route of Administration	Topical Ocular administration
Estimated Due Date of OCPB Review	Feb 08, 2003	Sponsor	Bausch & Lomb, Inc. Rochester, NY
PDUFA Due Date	July 08, 2004	Priority Classification	

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling				

NDA 21-675
Zylet (Loteprednol Etabonate 0.5%/Tobramycin 0.3% Suspension: DFS

Reference Bioanalytical and Analytical Methods	**X**			**LOQ — ıg/mL, Range — ng/mL**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X			Pooled Data
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:	Phase 2			**Protocol BLP 358-005**: A pilot, randomized, single-center comparison of the aqueous humor concentrations of Loteprednol Etabonate and Tobramycin Ophthalmic Suspension 0.5%/0.3% (LET) compared to Lotemax (loteprednol etabonate ophthalmic suspension, 0.5%) at two time points (20 and 40 minutes) in an ocular penetration model in approximately 40 subjects undergoing cataract surgery.
Phase 3 clinical trial:				**Protocol BLP 358-006**: A randomized, double-masked, multi-center comparison of the aqueous humor concentration of *Loteprednol* Etabonate , at two time points 40 and 60 minutes following administration of Bausch & Lomb Loteprednol Etabonate and Tobramycin Ophthalmic Suspension, 0.5%/0.3% or Lotemax (Loteprednol Etabonate Ophthalmic Suspension, 0.5%) during routine cataract surgery, N=2788. **Protocol BLP 358-004:** A randomized, double-masked, placebo-controlled comparison of the **clinical bioequivalence** of Bausch & Lomb Pharmaceuticals, Inc. Loteprednol Etabonate and Tobramycin Ophthalmic Suspension, 0.5%/0.3% compared to Lotemax in volunteers exposed to allergen challenge.
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				

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Zylet (Loteprednol Etabonate 0.5%/Tobramycin 0.3% Suspension: DFS

Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		3		

Filability and QBR comments

	"X" *if yes*	Comments
Application filable?	*YES*	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	• *What are the properties of the formulation of the drug product? What are the differences between clinical and to-be-marked formulations?* • Are the active moieties in the aqueous humor appropriately identified and measured to assess pharmacokinetic parameters and bioequivalence? • **Are analytical methods sensitive enough to determine the extent of loteprednol absorption after topical ophthalmic administration?** • **Should bioavailability assessment of tobramycin following ophthalmic administration of the test product be done? Why/why not?** • **Is there a need to measure systemic exposure of loteprednol and tobramycin following ophthalmic administration?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Chandra S. Chaurasia, Ph. D.**	
Secondary reviewer Signature and Date	**E. Dennis Bashaw, Pharm. D.**	

NDA 21-675
Zylet (Loteprednol Etabonate 0.5%/Tobramycin 0.3% Suspension: DFS

Chandra S. Chaurasia, Ph.D. /S/ Date: _____
Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. /S/ Date: _____

CC: NDA 21-675, HFD-850 (P. Lee), HFD-550 (R. Rodriguez), HFD-880 (D. Bashaw, J. Lazor, A. Selen)

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/s/

Chandra S. Chaurasia
6/15/04 02:45:07 PM
BIOPHARMACEUTICS

Dennis Bashaw
6/15/04 05:42:46 PM
BIOPHARMACEUTICS