CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020809

STATISTICAL REVIEW(S)

SSC - Holmes

Statistical Review and Evaluation

MAR 4 1997

NDA:	**20-809 [Related IND 49,156] under 505(b)(2)**
Drug Class:	**Topical Ophthalmic Solution**
Name of Drug:	**Diclofenac Sodium Ophthalmic Solution 0.1%**
Applicant:	**Alcon Laboratories, Inc. 6201 S. Freeway, Fort Worth, Texas 76134 (817) 293-0450**
Submission Date:	**December 23, 1996**
Review Date:	**March 04, 1997**
Indications:	**Treatment of Postoperative Inflammation following Cataract Surgery**
Studies:	**Controlled Clinical: C95-16 and C95-07**
Statistical Reviewer:	**Lillian Patrician, MS, MBA**
Applicant Contact Person:	**Susan Caballa, Assoc. Dir, Regulatory Affairs (817) 568-6296 Robert Roehrs (817) 551-8764**

I. Background

This review is an evaluation of U.S. Clinical Studies C95-07 and C95-16, the results of which were submitted for the use of Diclofenac Sodium 0.1% ophthalmic solution (DS) in the treatment of postoperative inflammation following cataract surgery. The sponsor's objective is to market this agent with a therapeutically equivalent rating (AB) to Voltaren Ophthalmic of Ciba Vision Ophthalmics, who markets its topical ophthalmic formulation in Canada, the United States, and Europe for the treatment of postoperative inflammation in patients who have undergone cataract extraction. ***[Attachment # 1 - Page 6]***

DS is a nonsteroidal, anti-inflammatory drug (NSAID) with analgesic and antipyretic activity. The agent, which is one of a series of phenylacetic acids, is being submitted under Section 505(b)(2) because the active ingredient, diclofenac sodium, is not a new molecular entity (has been approved under NDA19-201 for Voltaren tablets, and NDA 20-037 for Voltaren Ophthalmic solution). The sponsor reports that other studies relied upon by the sponsor were not conducted by or for the sponsor, and the sponsor has not obtained a right of reference or use from those who conducted the investigations.

II. Study C95-07

Study Design: The sponsor developed Study C95-07 to determine the safety and efficacy of Diclofenac Sodium 0.1% ophthalmic solution (DS) in treating post-surgical ocular inflammation. This was a Phase 3, randomized, multi-center, parallel-group, 3-arm, triple-masked, therapeutic equivalence study comparing DS to Voltaren 0.1% Ophthalmic and Vehicle Control. Under a randomization schema of 1:1:1, 370 cataract patients were enrolled in 18 U.S. centers as 126 DS; 123 Voltaren; and 121 Vehicle. These patients had moderate to severe anterior chamber cells and flare following cataract surgery. By end of study, the sponsor deemed 352 patients (120 DS; 117 Voltaren; 115 Vehicle) evaluable for a "per protocol" efficacy analysis in that they met inclusion/exclusion criteria, received at least one dose of study medication, and returned for follow-up or were deemed a therapeutic failure.

There were 11 scheduled visits of the study: Presurgical eye exam across Visits 1 - 5; Surgery and Post-op exam across Visits 6 - 7; Baseline Day 1 (22-34 hours post-surgery) as Visit 8; Day 4 (+/ - 1 day) as Visit 9; Day 8 (+/ - 1 day) as Visit 10; and Day 15 (+/ - 1 day) as Visit 11.

On Baseline Day 1, if a patient qualified for inclusion (sum of anterior chamber cells and flare had to be greater than or equal to 4, and the anterior chamber flare count had to be at least 2), he was then randomized to one of the three treatment arms. One drop of study medication was instilled q.i.d. in the operated eye beginning 1 day post-surgery and continuing 14 days. No corticosteroids were allowed preoperatively, on day of surgery, or during study. The entire study began in March, 1996 and ended August, 1996. ***[Attachment # 1 - Page 6]***

The primary objective was to demonstrate clinical bioequivalence between DS 0.1% and Voltaren 0.1%. Efficacy variables were anterior chamber cells and flare measured by slit lamp biomicroscopy without pupil dilation on a scale of 0 to 4 [0=none; 1=mild (1-5 cells); 2=moderate (6-15 cells); 3=severe (16-30 cells); 4=very severe (greater than 30 cells)]. Secondary efficacy variables included the decrease in visual acuity and patient therapeutic failure rates. Treatment failures were defined as those patients who recorded at any follow-up visit the efficacy scores of the sum of anterior chamber cells and flare to be greater or equal to that recorded at baseline. Safety was evaluated by assessment of adverse experiences and intraocular pressure.

Sponsor's Evaluation: The sponsor analyzed the variables of ocular inflammation symptoms (anterior chamber cells and flare) by using a repeated measures analysis of variance model (SAS Version 6.10, Proc Mixed) to assess differences between DS and Voltaren 0.1%. Two-sided 95% confidence intervals for the difference between DS 0.1% and Voltaren 0.1% were used to show equivalence between the two treatments for both cells and flare. Equivalency was determined for any visits where the 95% confidence limits were within 20% of scale range for cells and flare. Treatment comparisons using percent of patients labeled as treatment failures were made via chi-square tests at each visit.

The sponsor performed a per protocol analysis for 352 (120 DS, 117 Voltaren, and 115 Vehicle) patients. By sponsor's determination these patients were evaluable for efficacy because they met inclusion/exclusion criteria; returned for follow-up visits; and received at least 1 dose of study medication. Eighteen patients (6 from each treatment arm) were excluded from the Intent-to-treat data set. They were DS: 1401, 1410, 3002, 3004, 7006, 8001; Voltaren: 304, 813, 1418, 1424,

3003, 7008; and Vehicle: 409, 427, 3001, 3005, 7002, 7004. ***[Attachment # 7 - Page 12]***

The sponsor determined that both Diclofenac sodium 0.1% and Voltaren 0.1% solution were more effective than Vehicle in reducing anterior chamber cells as assessed on Days 8 and 15, and that these demonstrated a statistically significant difference from Vehicle with a p-value < 0.05. Similarly, DS and Voltaren reduced anterior chamber flare more than did Vehicle for Days 4, 8, and 15 with a statistically significant difference demonstrated at a p-value < 0.01. The sponsor also concluded that DS and Voltaren were therapeutically equivalent, and that patients using either of these ophthalmic solutions had lower decrease in visual acuity than those in the Vehicle group ($p < 0.05$). The sponsor summarizes Diclofenac Sodium 0.1% ophthalmic solution as safe and effective in the treatment of ocular inflammation following cataract surgery.

Reviewer's Evaluation:

1. Primary Efficacy Variables The primary efficacy variables of ocular inflammation symptoms (anterior chamber cells and flare) were analyzed by using a repeated measures analysis of variance model to assess differences between DS and Voltaren 0.1%. Two-sided 95% confidence intervals for the difference between DS 0.1% and Voltaren 0.1% were used to evaluate equivalence between the two treatments for both cells and flare, as well as for the sum of cells and flare.

This Reviewer analyzed all patients in the Intent-to-treat (ITT) data set using last-observation-carried-forward for those visits with missing observations due to premature discontinuations or terminations from study. The total number of evaluable ITT patients became 369 (125 DS; 123 Voltaren; and 121 Vehicle) because DS-Patient #8001 under Investigator 1964 (Tripathi) discontinued from study as a protocol violation (Ocufen was given pre-operatively). Although this patient was included in the safety analysis, there were no efficacy measures taken, including no baseline values. The randomization schema provided a balance in the distribution of patients across the 3 treatment arms. The patients were also equally distributed by sex, iris color, and race. There was no significant variation per treatment-arm efficacy results across investigational centers, sex, age, race, or iris color. ***[Attachments # 2-4 - Pages 7-9]***

Three hundred nine patients (109 DS; 115 Voltaren; and 85 Vehicle) followed protocol and completed study, whereas 61 patients (17 DS; 8 Voltaren; and 36 Vehicle) discontinued or terminated due to adverse experiences, lack of efficacy, lost-to-followup, patient decision, and protocol violations. A secondary completers' analysis was compared to that of the ITT and showed results consistent with the ITT analysis. ***[Attachments # 8-10 - Pages 13-15]***

Two-sided 95% confidence intervals on the difference between treatment means (DS 0.1% and Voltaren 0.1%), as well as difference between treatment mean changes from baseline, were used to show equivalence between the two treatments for both cells and flare, and the sum of cells and flare. Results indicate that the difference in population means between DS 0.1% and Voltaren 0.1% range from _____ for all observation time points. Ninety-five percent of such confidence intervals derived from repeated random samples drawn from these populations would contain the true difference in population means. The range of likely values for the difference between these means is quite narrow (within 20% of scale range) and, because it includes zero, the null hypothesis that asserts a zero difference cannot be rejected. Therefore, Diclofenac Sodium 0.1% and Voltaren 0.1% are equivalent with regard to the measure of anterior chamber cells and flare in the treatment

of postoperative inflammation following cataract surgery. ***[Attachments # 8-9 - Pages 13-14]***

Graphical representation of treatment means and the treatment mean changes from baseline also indicate no differences between DS and Voltaren with respect to the sum of anterior chamber cells and flare. ***[Attachment # 11 - Page 16]***

2. **Secondary Efficacy Variables** Conjunctival erythema, ciliary flush, foreign body sensation, tearing and photophobia were not measured and not used as secondary variables. Instead therapeutic failure rates were evaluated.

This reviewer determined a higher therapeutic failure rate than that reported by the sponsor. After excluding 18 patients from the ITT, the sponsor defined only 15 therapeutic failures (1 DS; 1 Voltaren; and 13 Vehicle) in the per-protocol analysis. These therapeutic failures discontinued from study prematurely with discontinuation codes of "5" on the exit page of the case report form.

This reviewer's evaluation of the ITT data set determined 48 therapeutic failures [12 DS (10%); 6 Voltaren (5%); and 30 Vehicle (25%)] who were selected according to protocol definition, i.e., those patients who recorded at any follow-up visit the efficacy scores of the sum of anterior chamber cells and flare to be greater or equal to that recorded at baseline. Using chi-square tests to analyze treatment consistency per visit, comparisons of percentage of patients found to be treatment failures demonstrated statistically significant differences between DS and Vehicle, as well as between Voltaren and Vehicle. There was insufficient evidence to determine a statistically significant difference between DS and Voltaren with respect to therapeutic failures. The same results were shown for percentage of patients who completed study; 87% DS-treated patients, 93% Voltaren, and 70% Vehicle completed study. ***[Attachment # 8 - Page 13]***

3. **Safety Summary**

Of the 61 patients who terminated study prematurely, 31 were due to adverse experiences; an additional 15 were due to lack of efficacy (no improvement in anterior chamber cells and/or flare); and 6 were by patient decision. DS-treated patients who terminated due to adverse experiences reported increased intraocular pressure; burning, redness, discharge; ciliary injection; wound infection; weakness; and limbal ulcer. Voltaren-treated patients reported increased IOP; wound leak; red eye, floaters; 3+ epithelial keratopathy; and superficial punctate keratopathy. ***[Attachments # 2-3 - Pages 7-8]***

An equal percentage of DS and Voltaren patients reported adverse experiences (29% DS and 28% Voltaren) compared to 49% Vehicle. Of these, 10% DS and 16% Voltaren patients reported experiences that were deemed treatment-related.

III. Other Studies

Phase I Comfort Study C95-17 compared Diclofenac Sodium Ophthalmic Solution 0.1% to Voltaren Ophthalmic Solution 0.1% in a double-masked, randomized, two-period, cross-over design of 20 healthy, normal volunteers. The sponsor reports that study results show DS to be equivalent to Voltaren with respect to ocular discomfort, membrane discomfort, and visual clarity. There were no adverse events reported.

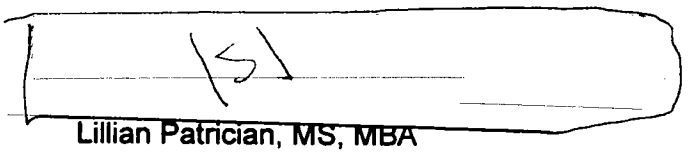
IV. Reviewer's Overall Comments

1. Summation of Findings:

Evaluation of the results of Study C95-07 are in agreement with the sponsor's. Both Diclofenac sodium 0.1% and Voltaren 0.1% solution demonstrated statistically significant differences over Vehicle in reducing anterior chamber cells as assessed on Days 8 and 15. Similarly, DS and Voltaren showed a statistically significant reduction in anterior chamber flare over that of Vehicle for Days 4, 8, and 15. The results also show that DS and Voltaren are therapeutically equivalent.

2. Data Considerations: The data sets provided by the sponsor included no patients enrolled for Investigators #1113 [Miller, UT]; #1427 [Wolf, OK]; and #2043 [Liss, PA]. Although the sponsor reports 19 centers, data were only available for a patient enrollment from 18 investigational centers. ***[Attachment # 1 - Page 6]***

V. There are No Comments to be Conveyed to the Sponsor.



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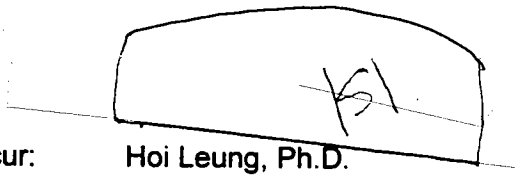

Concur: Hoi Leung, Ph.D.
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Archival: NDA 20-809

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This report has a total of sixteen [16] pages including 11 attachments.

Summary Data for All Protocols

Study	C95-07	C95-16
Design	Multi center, 3-arm, triple-masked, randomized, parallel comparison of DS versus Voltaren and Vehicle	Phase I Clinical Pharmacology, double-masked, randomized, 2-period, crossover comfort study of 0.1% DS vs. Voltaren
Objective	To evaluate ocular safety and efficacy of Diclofenac sodium 0.1% ophthalmic solution compared with Voltaren and Vehicle Control in the treatment of post-operative inflammation following cataract surgery.	To assess ocular safety and efficacy after topical instillation of single drop of DS 0.1% or Voltaren 0.1% to healthy, normal eyes.
Dates of Study Conduct	03/19/96 to 08/24/96	03/29/96 to 04/12/96
Duration	2 weeks	2 weeks
# Sites	18 (of 21) U.S. Centers: ******* 225 - Poirer, TX 271 - Stewart, TX 362 - Caldwell, LA 498 - McCulley, TX 501 - Friedlaender, CA 695 - Kraff, IL 750 - Olander, WI 847 - Brint, LA 970 - Lehmann, TX 1008 - Horwitz, TX 1113 - Miller, UT *** [zero enrollment] 1208 - Caine, VA 1229 - Crabb, TN 1300 - Assil, CA 1403 - Morris, CA 1427 - Wolf, OK *** [zero enrollment] 1499 - Jaffe, FL 1806 - Sall, CA 1832 - Goosey, TX 1964 - Tripathi, SC 2043 - Liss, PA *** [zero enrollment]	1 Alcon in-house clinic: 703 - Beasley, TX
Dose Regimen	One drop in surgical eye 4 times daily for 14 consecutive days beginning 22-34 hours following cataract surgery	One drop over one day
Primary Efficacy Measure	Reduction in Anterior Chamber Cells and Flare	Ocular discomfort, visual clarity, and burning profile (membrane discomfort composite variables)
Secondary Efficacy Measures	Therapeutic treatment failures and visual acuity	
Visit Schedule	Vst 1-5 =Eye Exam Screening Day -30 to -2 Visit 6 = Surgery Visit 7 = Surgery Postop Day 0 Visit 8 = Baseline Postop Day1 (22-34 hrs) Visit 9 = Day 4 Visit 10 = Day 8 Visit 11 = Day 15	Visit 1 = Baseline Visit 2 = 1-drop Instillation Treatment A [24-hour washout period] Visit 3 = 1-drop Instillation Treatment B Visit 4 = Slit-lamp and Visual Acuity
,lled	370 = 126 DS : 123 Voltaren : 121 Vehicle	20 healthy, adult volunteers

******* **The sponsor reports that was contracted as a contract research organization for interim monitoring and close-out visits at some sites.**

Summary Data

Reviewer's Results	Study C95-07		
Treatment Arms	DS	Voltaren	Vehicle
# Enrolled	126	123	121
# Safety-Evaluable	126	123	121
# Efficacy-Evaluable [ITT with LOCF]	125 **	123	121
# Completed Study	109	115	85
# Noncompleters	17/126 (14%)	8/123 (7%)	36/121 (30%)
# Terminated Study	17 (13%)	8 (7%)	36 (30%)
Due to AE	8 (6%)	4 (3%)	19 (16%) ***
Due to Treatment-related AE	3 (2%)	2 (2%)	13 (11%)
Due to Lack of Efficacy	1 (1%)	1 (1%)	13 (11%)
Lost to Follow-up	3 (2%)	2 (2%)	2 (2%)
Patient Decision	4 (3%)	0 (0%)	2 (2%)
Other (Protocol Violations)	1 (1%)	1 (1%)	0 (0%)
# Patients with Any AE ****	37/126 (29%)	35/123 (28%)	59/121 (49%)
With Treatment-related Ocular AE	12/126 (10%)	20/123 (16%)	24/121 (20%)
With Treatment-related AE	12/126 (10%)	21/123 (17%)	25/121 (21%)
# Males	44 (35%)	41 (33%)	44 (36%)
# Females	82 (65%)	82 (67%)	77 (64%)
# Age 30-39 Years	1	0	0
# Age 40-49 Years	2	2	7
# Age 50-99 Years	123	121	114
# Caucasian	87	87	83
# Black	26	26	26
# Other	13	10	12
# with Light Iris Color	52	54	55
# with Dark Iris Color	74	69	66

** The total number of efficacy-evaluable ITT patients is 369. DS-Patient #8001 under Investigator 1964 (Tripathi) was a 75-year old white male who was discontinued from study because Ocufen was given pre-operatively. Although this patient was included in the safety analysis, there were no efficacy measures taken, including no baseline values.

*** 4/44 (9%) male patients and 15/77 (19%) female patients in the vehicle group discontinued due to adverse experiences.

**** Data on adverse experience incidence is taken from sponsor's summary [Vol 11.8.0171 and 11.8.0245].

Patients Who Did Not Complete Study

Reviewer's Results		Study C95-07		
Type of Exit	Comments	DS	Voltaren	Vehicle
Terminated [Lack of Efficacy]	No Improvement in Cells and/or Flare	1	1	13
Terminated for Adverse Event	Increase in IOP	2	1	0
Terminated for Adverse Event	Burning, Redness, Discharge	2	0	4
Terminated for Adverse Event	Ciliary Injection	1	0	0
Terminated for Adverse Event	2+ Conjunctival Injection	0	0	5
Terminated for Adverse Event	Wound Infection	1	0	0
Terminated for Adverse Event	Weakness, Shakiness, UTI	1	0	0
Terminated for Adverse Event	Limbal Ulcer	1	0	0
Terminated for Adverse Event	Wound Leak	0	1	0
Terminated for Adverse Event	Red Eye, Floaters	0	1	0
Terminated for Adverse Event	3+ Epithelial Keratopathy	0	1	0
Terminated for Adverse Event	Superficial Punctate Keratopathy	0	1	0
Terminated for Adverse Event	Secretion	0	0	1
Terminated for Adverse Event	Discomfort and Photophobia	0	0	1
Terminated for Adverse Event	Persistent Foreign Body Sensation	0	0	2
Terminated for Adverse Event	Uveitis	0	0	1
Terminated for Adverse Event	Post-op Inflammation	0	0	1
Terminated for Adverse Event	Corneal Edema	0	0	1
Terminated for Adverse Event	Hyphemia	0	0	1
Terminated for Adverse Event	Allergic Conjunctivitis and Pain	0	0	1
Terminated for Adverse Event	Pupillary Block Glaucoma	0	0	1
Discontinued	Lost to Follow-up	3	2	2
Discontinued	Patient Decision	4	0	2
Discontinued	Protocol Violation [Ocufen used Pre-op]	1	0	0
Discontinued	Protocol Violation [use of topical steroid]	0	1	0
Total Noncompleters = 61		17	8	36

Distribution of Patients Who Discontinued/Terminated Attachment # 4

By Days To Discontinuation

(Reviewer's Results)

NDA 20-809 PROTOCOL C9507 [:\N20809.WPD]
TAB9 - DATA=DISCSIGN - DISCONTINUATION INFO

Reviewer's Results		TRT DS #	TRT VOL #	TRT PBO #	TOTAL #
TOTAL		126	123	121	370
Reason for discontinuing treatment	VISIT ID CODES				
ADVERSE EVENT	DAY 15	6	3	10	19
	UNSCHED-1	1	0	8	9
	UNSCHED-2	1	1	1	3
LOST TO FOLLOW-UP	DAY 15	2	1	2	5
	UNSCHED-1	1	1	0	2
PATIENT DECISION	DAY 15	4	0	2	6
TREATMENT FAILURE	DAY 15	1	1	11	13
	UNSCHED-1	0	0	2	2
OTHER	DAY 15	1	1	0	2
REASON OTHER TEXT					
OCUFEN USED PRE-OP.		1	0	0	1
USE OF TOPICAL STEROID/WITHIN 30D OF BASELINE		0	1	0	1

APPEARS THIS WAY
ON ORIGINAL

Patient Distribution by Investigational Site - All Patients Enrolled

Reviewer's Results							Mean Sum of Anterior Chamber Cells and Flare											
Study C95-07	# Enrolled			# Non-Completers			Baseline			Day 4			Day 8			Day 15		
Investigator	DS	VOL	PBO	DS	VOL	PBO	DS	VOL	PBO	DS	VOL	PBO	DS	VOL	PBO	DS	VOL	PBO
225 Poirer, TX	1	1	1	1	0	1	5.0	4.0	4.0	2.0	3.0	1.0	3.0	1.0	0.0	0.0	0.0	0.0
271 Stewart, TX	13	13	13	0	1	2	6.6	6.1	6.2	6.6	6.5	7.1	6.1	4.8	6.5	4.8	3.3	5.5
362 Caldwell, LA	4	4	3	2	0	2	5.0	5.0	4.3	4.0	3.8	3.0	1.8	1.8	3.0	0.5	0.8	3.0
498 McCulley, TX	3	3	3	0	0	0	6.7	7.7	6.0	6.0	6.7	5.7	5.0	6.0	4.3	4.0	3.3	3.3
501 Friedlaender, CA	2	1	2	0	0	0	6.0	4.0	5.0	6.0	2.0	2.0	3.0	0.0	2.0	1.5	0.0	0.5
695 Kraff, IL	3	4	3	0	1	2	4.7	5.8	4.0	3.7	5.3	4.3	2.3	4.3	4.0	2.3	2.3	5.0
750 Olander, WI	7	8	7	1	1	3	4.6	4.5	4.3	2.6	2.8	3.1	2.4	2.1	3.1	1.7	1.9	2.0
847 Brint, LA	4	4	4	0	0	3	4.0	4.5	4.0	1.5	2.3	1.8	1.5	1.5	5.3	0.0	0.0	0.0
970 Lehmann,TX	18	17	17	2	0	5	4.6	4.4	4.1	3.1	2.9	3.6	2.1	1.8	3.8	1.1	0.5	2.4
1008 Horwitz, TX	4	5	4	1	0	2	5.5	5.6	5.0	3.0	3.2	3.3	2.7	2.0	5.0	1.3	1.0	3.5
1208 Caine, VA	3	2	2	0	0	2	4.0	4.0	4.0	1.7	2.0	3.0	1.0	2.0	3.0	0.3	1.0	0.0
1229 Crabb, TN	18	17	17	1	1	1	4.5	4.6	4.6	3.4	3.0	4.1	2.2	1.9	3.2	1.1	1.1	2.5
1300 Assil, CA	7	6	7	2	0	3	5.1	4.3	4.9	4.3	2.8	3.5	1.2	1.3	2.3	0.6	0.8	0.5
1403 Morris, CA	9	9	9	2	1	3	4.4	4.1	4.8	2.0	1.9	2.0	1.6	0.9	1.8	0.9	0.9	1.7
1499 Jaffe, FL	10	10	10	2	2	3	4.9	4.6	5.3	2.3	1.8	4.4	1.4	1.5	2.2	0.9	0.6	1.4
1806 Sall, CA	12	12	12	2	1	2	6.0	6.2	6.5	5.0	5.1	6.0	4.4	4.2	5.3	3.6	2.7	3.8
1832 Goosey, TX	7	7	7	0	0	2	6.6	5.9	5.7	6.4	6.0	6.7	5.0	6.1	6.0	3.1	4.0	4.4
1964 Tripathi, SC	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Mean Sum of Anterior Chamber Cells and Flare by Demographic Distribution

Study C95-07 All Patients Enrolled

Reviewer's Results							Mean Sum of Anterior Chamber Cells and Flare											
	# Enrolled			# Non-completers			Baseline			Day 4			Day 8			Day 15		
Study C95-07	DS	VOL	PBO	DS	VOL	PBO	DS	VOL	PBO	DS	VOL	PBO	DS	VOL	PBO	DS	VOL	PBO
# Males	44	41	44	8	2	10	5.1	4.9	4.9	4.0	3.5	4.4	3.2	2.5	4.3	2.1	1.4	3.1
# Females	82	82	77	9	6	26	5.2	5.1	5.1	3.8	3.8	4.2	2.8	2.8	3.7	1.8	1.6	2.7
# Age 30-39 Years	1	0	0	0	0	0	6.0	0.0	0.0	5.0	0.0	0.0	5.0	0.0	0.0	5.0	0.0	0.0
# Age 40-49 Years	2	2	7	0	0	4	7.0	6.5	5.0	7.0	6.0	3.9	5.5	5.0	5.6	4.5	4.0	3.7
# Age 50- 99 Years	123	121	114	17	8	32	5.1	5.0	5.0	3.8	3.7	4.3	2.8	2.6	3.8	1.8	1.5	2.9
# Caucasian	87	87	83	13	6	31	5.0	4.9	4.8	3.7	3.6	4.0	2.8	2.6	3.6	1.9	1.4	2.6
# Black	26	26	26	2	2	3	5.0	5.2	5.2	3.8	3.9	4.7	2.6	2.6	4.4	1.3	1.7	3.4
# Other	13	10	12	2	0	2	6.2	5.8	59	5.0	4.4	5.3	4.5	3.3	4.7	3.5	2.3	3.1
# with Light Iris Color	52	54	55	--	--	--	5.1	4.9	4.8	3.8	3.7	4.1	3.0	2.6	3.7	1.8	1.4	2.6
# with Dark Iris Color	74	69	66	--	--	--	5.2	5.2	5.2	3.9	3.7	4.5	2.8	2.7	4.1	2.0	1.7	3.1

Mean Change from Baseline Efficacy Scores Per Treatment, and Visit

Patients Evaluable Per Protocol using Last-Observation-Carried Forward

[Reported in Vol 11.8.0152 - .0233]

Sponsor's Results		Study C95-07							
		DS	Voltaren	Placebo	DS / VOL	DS	Voltaren	Placebo	DS - VOL
# Enrolled		126 ***	123	121					
# Excluded from Efficacy		6	6	6					
# Non-completers	Due to AE, Lost-to-FUP, Pat Decision, Treatment Failures, Other	17	8	36					
# Evaluable "Per Protocol"		120	117	115					
% Treatment Failures	By End-of-Study	1/126	1/123	13/121					
		Mean [n]	Mean [n]	Mean [n]	p-value	Mn BL Change	Mn BL Change	Mn BL Change	n_{trt} [95% C.I.] $diff_{trt}$
Anterior Chamber Cells	Visit 4 [Baseline Post-op Day 1]	2.8 [120]	2.7 [117]	2.7 [115]	0.53				Difference in Treatment LSMeans
	Visit 5 [Day 4]	2.3	2.2	2.4	0.75	-0.5	-0.5	-0.3	248 [-0.34, 0.21] 0.07
	Visit 6 [Day 6-8 / Week 1]	1.9	1.7	2.2	0.41	-0.9	-1.0	-0.5	248 [-0.40, 0.15] 0.13
	Visit 7 [Day 14-16 / Week 2]	1.2	1.0	2.0	0.24	-1.6	-1.7	-0.7	248 [-0.47, 0.09] 0.19
		Mean [n]	Mean [n]	Mean [n]	p-value	Mn BL Change	Mn BL Change	Mn BL Change	n_{trt} [95% C.I.] $diff_{trt}$
Anterior Chamber Flare	Visit 4 [Baseline Post-op Day 1]	2.3	2.3	2.3	0.88				Difference in Treatment LSMeans
	Visit 5 [Day 4]	1.5	1.5	1.9	0.63	-0.8	-0.8	-0.4	248 [-0.30, 0.13] 0.08
	Visit 6 [Day 6-8 / Week 1]	1.1	1.0	1.7	0.46	-1.2	-1.2	-0.6	248 [-0.28, 0.14] 0.07
	Visit 7 [Day 14-16 / Week 2]	0.7	0.6	1.4	0.30	-1.6	-1.7	-0.9	248 [-0.34, 0.09] 0.12

Comparison between Mean Ocular Severity Scores and Differences in Treatment Means

Intent-to-Treat Analysis using Last-Observation-Carried-Forward

Reviewer's Results	Study C95-07						
	DS	Voltaren	Placebo	DS/VOL	DS/ PBO	VOL/PBO	DS - VOL
# Enrolled	126	123	121				n_{trt} [95% C.I.] $diff_{trt}$
Sum of Cells and Flare	Mean [n]	Mean [n]	Mean [n]	p-value	p-value	p-value	Difference in Treatment Means
Visit 4 [Baseline Post-op Day 1]	5.2 [125]	5.0 [123]	5.0 [121]				
Visit 5 [Day 2-4]	3.9 [125]	3.7 [123]	4.3 [121]	0.5400	0.0789	0.0202	248 [-0.33, 0.62] 0.15
Visit 6 [Day 6-8 / Week 1]	3.0 [125]	2.8 [123]	3.9 [121]	0.4749	0.0009	0.0001	248 [-0.33, 0.70] 0.19
Visit 7 [Day 14-16 / Week 2]	2.1 [125]	1.8 [123]	3.3 [121]	0.1443	0.0001	0.0002	248 [-0.12, 0.83] 0.36
Anterior Chamber Cells	Mean [n]	Mean [n]	Mean [n]	p-value	p-value	p-value	Difference in Treatment Means
Visit 4 [Baseline Post-op Day 1]	2.8	2.7	2.8				
Visit 5 [Day 2-4]	2.3	2.2	2.4	0.6405	0.3691	0.1615	248 [-0.22, 0.36] 0.07
Visit 6 [Day 6-8 / Week 1]	1.9	1.7	2.2	0.4027	0.0315	0.0076	248 [-0.15, 0.43] 0.13
Visit 7 [Day 14-16 / Week 2]	1.3	1.1	2.0	0.1249	0.0008	0.0001	248 [-0.06, 0.52] 0.23
Anterior Chamber Flare	Mean [n]	Mean [n]	Mean [n]	p-value	p-value	p-value	Difference in Treatment Means
Visit 4 [Baseline Post-op Day 1]	2.3	2.3	2.3				
Visit 5 [Day 2-4]	1.6	1.5	1.9	0.5082	0.0189	0.0031	248 [-0.19, 0.32] 0.08
Visit 6 [Day 6-8 / Week 1]	1.1	1.0	1.7	0.6533	0.0001	0.0001	248 [-0.19, 0.30] 0.06
Visit 7 [Day 14-16 / Week 2]	0.8	0.7	1.3	0.2445	0.0001	0.0001	248 [-0.09, 0.34] 0.13
Proportion of Therapeutic Failures							
Visit 5 [Day 2-4]	42/126 [33%]	35/123 [28%]	62/121 [51%]	0.405	0.004	0.001	
Visit 6 [Day 6-8 / Week 1]	23/126 [18%]	17/123 [14%]	44/121 [36%]	0.341	0.001	0.001	
Visit 7 [Day 14-16 / Week 2]	12/126 [10%]	6/123 [5%]	30/121 [25%]	0.157	0.001	0.001	
Proportion of Non-completers	17/126 [13%]	8/123 [7%]	36/121 [30%]	0.067	0.002	0.001	

Comparison between Mean Change from Baseline and Differences in Mean Changes from Baseline for Efficacy Scores

Intent-to-Treat Analysis using Last-Observation-Carried-Forward

Reviewer's Results	Study C95-07						
	DS	Voltaren	Placebo	DS/VOL	DS/ PBO	VOL/PBO	DS - VOL
# Enrolled	126	123	121				n_{trt} [95% C.I.] $diff_{trt}$
BL Change in Sum of Cells and Flare	Mean [n]	Mean [n]	Mean [n]	p-value	p-value	p-value	Difference in Trt Changes from BL
Visit 5 [Day 2-4]	-1.3 [125]	-1.3 [123]	-0.7 [121]	0.8687	0.0033	0.0017	248 [-0.32, 0.38] 0.03
Visit 6 [Day 6-8 / Week 1]	-2.2 [125]	-2.3 [123]	-1.2 [121]	0.7333	0.0001	0.0001	248 [-0.32, 0.46] 0.07
Visit 7 [Day 14-16 / Week 2]	-3.0 [125]	-3.3 [123]	-1.7 [121]	0.2494	0.0001	0.0001	248 [-0.18, 0.64] 0.08
BL Change in Anterior Chamber Cells	Mean [n]	Mean [n]	Mean [n]	p-value	p-value	p-value	Difference in Trt Changes from BL
Visit 5 [Day 2-4]	-0.5 [125]	-0.5 [123]	-0.3 [121]	0.8227	0.0775	0.1027	248 [-0.23, 0.15] -0.03
Visit 6 [Day 6-8 / Week 1]	-0.9 [125]	-0.9 [123]	-0.6 [121]	0.7389	0.0075	0.0022	248 [-0.19, 0.27] 0.04
Visit 7 [Day 14-16 / Week 2]	-1.5 [125]	-1.6 [123]	-0.8 [121]	0.2590	0.0001	0.0001	248 [-0.10, 0.38] 0.14
BL Change in Anterior Chamber Flare	Mean [n]	Mean [n]	Mean [n]	p-value	p-value	p-value	Difference in Trt Changes from BL
Visit 5 [Day 2-4]	-0.8 [125]	-0.8 [123]	-0.4 [121]	0.6070	0.0011	0.0002	248 [-0.20, 0.26] 0.05
Visit 6 [Day 6-8 / Week 1]	-1.3 [125]	-1.3 [123]	-0.6 [121]	0.7879	0.0001	0.0001	248 [-0.16, 0.24] 0.03
Visit 7 [Day 14-16 / Week 2]	-1.5 [125]	-1.6 [123]	-0.9 [121	0.3546	0.0001	0.0001	248 [-0.11, 0.31] 0.10

Mean Ocular Severity Scores and Mean Change from Baseline Per Treatment and Visit

Completers Analysis

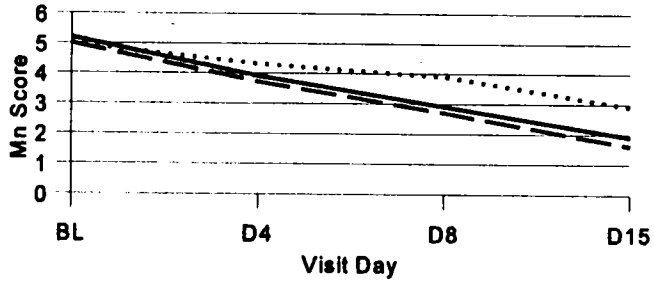
Reviewer's Results	Study C95-07											
	DS	Voltaren	Placebo	DS/VOL	DS/ PBO	VOL/PBO	DS	Voltaren	Placebo	DS/VOL	DS/ PBO	VOL/PBO
# Enrolled	126	123	121									
Sum of Cells and Flare	Mean [n]	Mean [n]	Mean [n]	p-value	p-value	p-value	Mean Change	Mean Change	Mean Change	p-value	p-value	p-value
Visit 4 [Baseline Post-op Day 1]	5.2 [125]	5.0 [123]	5.0 [121]									
Visit 5 [Day 2-4]	3.9 [122]	3.7 [120]	4.3 [119]	0.5387	0.0849	0.0219	-1.3	-1.4	-0.7	0.8648	0.0028	0.0014
Visit 6 [Day 6-8 / Week 1]	2.9 [119]	2.7 [118]	3.9 [106]	0.3518	0.0004	0.0001	-2.3	-2.3	-1.1	0.7586	0.0001	0.0001
Visit 7 [Day 14-16 / Week 2]	1.9 [109]	1.6 [115]	2.9 [85]	0.1338	0.0005	0.0001	-3.3	-3.4	-2.2	0.3872	0.0001	0.0001
Anterior Chamber Cells	Mean [n]	Mean [n]	Mean [n]	p-value	p-value	p-value	Mean Change	Mean Change	Mean Change	p-value	p-value	p-value
Visit 4 [Baseline Post-op Day 1]	2.8 [125]	2.7 [123]	2.8 [121]									
Visit 5 [Day 2-4]	2.3 [122]	2.2 [120]	2.4 [119]	0.6802	0.3691	0.2025	-0.5	-0.5	-0.3	0.8234	0.0722	0.0955
Visit 6 [Day 6-8 / Week 1]	1.8 [119]	1.7 [118]	2.2 [106]	0.3660	0.0315	0.0023	-1.0	-1.0	-0.6	0.8351	0.0029	0.0012
Visit 7 [Day 14-16 / Week 2]	1.2 [109]	1.0 [115]	1.8 [85]	0.1976	0.0008	0.0001	-1.6	-1.7	-1.0	0.4205	0.0001	0.0001
Anterior Chamber Flare	Mean [n]	Mean [n]	Mean [n]	p-value	p-value	p-value	Mean Change	Mean Change	Mean Change	p-value	p-value	p-value
Visit 4 [Baseline Post-op Day 1]	2.3 [125]	2.3 [123]	2.3 [121]									
Visit 5 [Day 2-4]	1.6 [122]	1.5 [120]	1.9 [119]	0.4618	0.0179	0.0022	-0.8	-0.8	-0.4	0.6005	0.0009	0.0001
Visit 6 [Day 6-8 / Week 1]	1.1 [119]	1.0 [118]	1.7 [106]	0.4081	0.0001	0.0001	-1.3	-1.3	-0.5	0.7300	0.0001	0.0001
Visit 7 [Day 14-16 / Week 2]	0.7 [109]	0.6 [115]	1.1 [85]	0.1153	0.0022	0.0001	-1.7	-1.7	-1.2	0.4848	0.0001	0.0001

Mean Severity Scores and Mean Change from Baseline in Severity Scores
Completers Analysis By Treatment and By Sex

(Reviewer's Results)

Study C95-07

Mean Sum of Anterior Chamber Cells and Flare



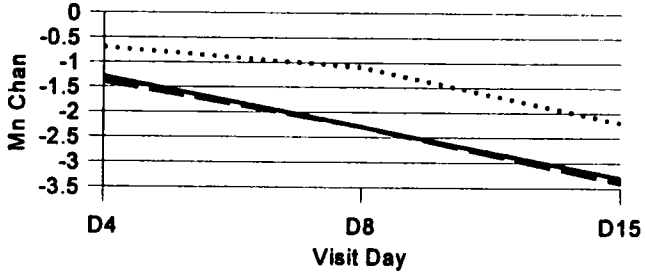
Completers: D4 [361] D8 [343] D15 [309]

——— DS — — — Voltaren

····· Vehicle

Study C95-07

Mean BL Change [Cells + Flare]



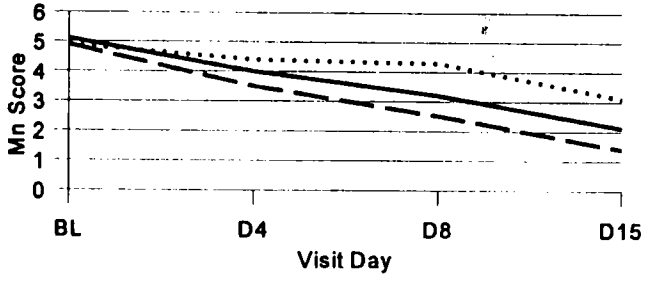
Completers: D4 [361] D8 [343] D15 [309]

——— DS — — — Voltaren

····· Vehicle

Study C95-07

Mean Sum of Anterior Chamber Cells and Flare



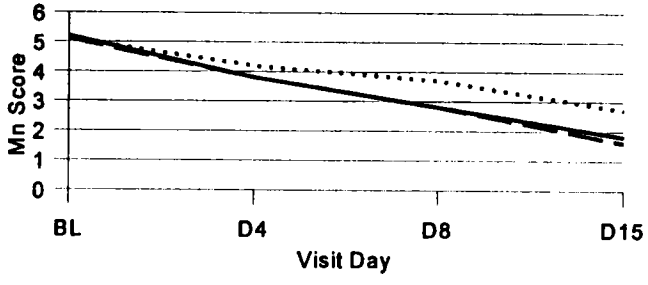
MALES [N=129]

——— DS — — — Voltaren

····· Vehicle

Study C95-07

Mean Sum of Anterior Chamber Cells and Flare



FEMALES [N=241]

——— DS — — — Voltaren

····· Vehicle

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020809

MICROBIOLOGY REVIEW(S)

HFD 550
Adams

MAR 4 1997

REVIEW FOR HFD-550
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1
4 March 1997

A. 1. NDA 20-809
APPLICANT: Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, TX 76134-2099

2. PRODUCT NAME: Diclofenac Sodium Ophthalmic Solution 0.1%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile ophthalmic solution for instillation into the eye.

4. METHODS OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The drug product is a non-steroidal antiinflammatory drug.

B. 1. DATE OF INITIAL SUBMISSION: 20 December 1996

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: 6 January 1997

C. REMARKS: The product is manufactured at the applicant's Fort Worth facility.

D. CONCLUSIONS: The application is recommended for approval on the basis of sterility assurance.

/S/ 4 March 1997
Paul Stinavage, Ph.D.

cc: Original NDA 20-809
HFD-550/H. Patel/J. Holmes
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 4 March 1997
R/D initialed by P. Cooney /S/ 3/4/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020809

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 20-809 **SUBMISSION DATE:** 12/20/96, 1/6/97 1/17/97

PRODUCT: Diclofenac Sodium Ophthalmic Solution 0.1%

SPONSOR: Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texax 76134-2099

REVIEWER: Dan Wang, Ph.D.

TYPE OF SUBMISSION: Original

BACKGROUND

The applicant submitted this NDA for Diclofenac Sodium Ophthalmic Solution 0.1%. This product is intended for the use in treatment of postoperative inflammation in patients who have undergone cataract extraction. Diclofenac Sodium is currently on the market as Voltaren tablets by Geigy (NDA 19-201) and Voltaren Ophthalmic solution by Ciba Vision Ophthalmics (NDA 20-037). The product that is the subject of this NDA contains the same amount of active ingredient as the approved Voltaren Ophthalmic solution - 0.1% diclofenac sodium, but there are differences in the inactive ingredients between these two products (See attached). The proposed package insert is based on the package insert for Voltaren Ophthalmic solution. The pharmacokinetics portion of the label is supported by studies originally submitted by Ciba-Geigy in NDA 19-201 and NDA 20-037. The applicant has not undertaken any PK trials of the proposed product. In the review process, it was found that the three PK studies that supported the PK pharmacokinetics portion of NDA 20-037 package insert were never reviewed by the PK reviewer. Those studies were reviewed by the Medical Officer.

In this NDA, the applicant requests a waiver from the requirements for submission of human *in vivo* bioavailability data according to the criteria set forth in 21 CFR 320.22 (b)(2). Consulting of 21 CFR indicates that the product that is the subject of this NDA does not fit the criteria of 320.22 (b)(2), which is only for inhalation product.

According to the package insert of Voltaren tablet, the volume of distribution of diclofenac sodium is 550 ml/kg (38.5 L for a 70 kg man) and the half-life is about 2 hours. The recommended dose in the proposed package insert is 1 drop (0.05 ml) in the affected eye four times daily beginning 24 hours after cataract surgery. The maximum dose is therefore 0.4 to 0.8 ml 0.1% diclofenac, i.e. 0.4 to 0.8 mg per day. Considering the large volume distribution and small dose, it is very likely to have a plasma concentration around or below the limit of quantitation (5 or 10 ng/ml), assuming 100% absorption.

COMMENT

1. In proposed package insert, the applicant cited bioavailability study results from Voltaren Ophthalmic (Ciba Vision Ophthalmics)'s package insert as if the applicant themselves conducted the study. This is considered misleading by the Agency. The applicant should re-write the paragraph by either referencing published data on diclofenac pharmacokinetics

following ophthalmic dosing or providing in the label an explanation as to why plasma levels would not be detected.

RECOMMENDATION

(1) As mentioned in the BACKGROUND section, it is not appropriate to use the criteria set forth in 21 CFR 320.22 (b)(2) for the product that is the subject of this NDA to request a waiver from the requirements for submission of human *in vivo* bioavailability data. The criteria of 320.22 (b)(2) is only for inhalation product, and as such is not relevant to this situation. However, based on the available published pharmacokinetic knowledge on diclofenac tablets, the proposed dose of diclofenac sodium ophthalmic solution is not likely to produce a quantifiable plasma level. Therefore, human *in vivo* bioavailability study is not required for this NDA. The applicant should be informed of COMMENT #1.

/S/ 12/24/97

Dan Wang
Division of Pharmaceutical Evaluation III

FT initialed by D. Bashaw, Pharm.D. /S/ 12/24/97

cc:
NDA 20-809 (Original)
HFD-550(Holmes)
HFD-880(N. Fleischer)
HFD-880(Bashaw)
HFD-880(Wang)
HFD-850(Mira Millison, Drug, Chron Files)
HFD-344(Viswanathan)

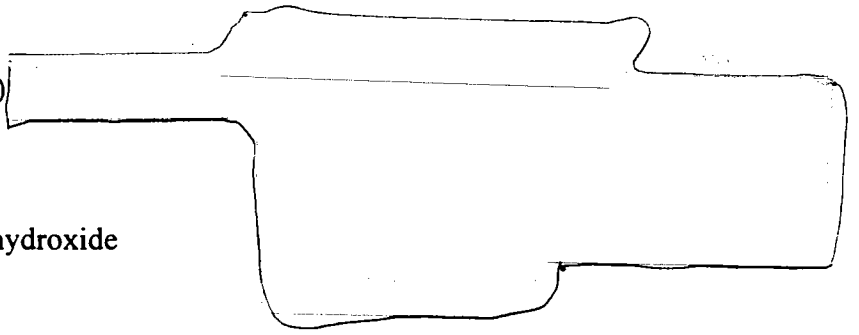
Diclofenac Sodium Ophthalmic Solution 0.1%

Active ingredient
Diclofenac sodium, 0.1%

Inactive ingredient
POLYQUAD® (polyquaternium-1)
Tocophersolan
Boric acid
Mannitol
Hydrochloric acid and/or sodium hydroxide
Purified water

Voltaren Ophthalmic® Solution, 0.1%

Active ingredient
Diclofenac sodium, 0.1%



APPEARS THIS WAY
ON ORIGINAL