CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020809

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 20-809
Original

NDA # 20-809		Submission:	12/20/97
		Receive date:	12/23/97
M.O. Review #44A		Review completed:	3/30/97

Drug name:	Diclofenac sodium ophthalmic solution, 0.1%
Generic name:	Diclofenac sodium
Proposed trade name:	Diclofenac Sodium Ophthalmic Solution, 0.1%
Chemical name:	A. Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-Monosodium salt B. Sodium [o-(2,6-dichloroanilino)phenyl]acetate
Sponsor:	Alcon Laboratories, Inc. 6201 South Freeway Fort Worth, TX 76134-2099
Pharmacologic Category:	Non-steroidal Anti-inflammatory
Proposed Indication(s):	Treatment of postoperative inflammation in patients who have undergone cataract extraction.
Dosage Form and Route of Administration:	Topical, ophthalmic solution
NDA Drug Classification:	5-S
Related Drugs:	Voltaren Ophthalmic® NDA 20-037- Approved 12/31/90 Voltaren® (tablets) NDA 19-201- Approved 7/28/88

2 Table of Contents

3 Material Reviewed
NDA Volumes 1-6; 9-11; 14

4 Chemistry/Manufacturing Controls
See Chemist's Review

Comparison of Diclofenac and Voltaren Formulations

Ingredient (mg/mL)	Diclofenac	Voltaren
Diclofenac Sodium		
Boric Acid		
Purified Water		
Polyquaternium-1		
Tocophersolan		
Mannitol		
Sodium Hydroxide and/or Hydrochloric Acid	Adjust pH	

5 Animal Pharmacology/Toxicology
See Pharmacology and Toxicology Reviews

Clinical Background

6.1 Relevant human experience

Postoperative inflammation is induced by trauma to the eye associated with the surgical procedures of cataract extraction. Surgically-induced iritis, which is usually minimal and self-limited, follows even the most uneventful cataract extraction. Although postsurgical inflammation associated with routine cataract extraction is generally mild, the eye is often uncomfortable and the external ocular tissues are irritated and inflamed. The clinical features of this common postoperative response include the presence of protein (flare) and leukocytes (cells) within the anterior chamber, engorgement of iris and conjunctival vessels, and minimal miosis. In clinical practice, the resolution of postoperative inflammation is monitored by observing changes in anterior chamber cells and flare during the days following surgery, with a slit-lamp biomicroscope or with a laser flare-cellmeter. Topically applied anti-inflammatory agents are routinely employed following cataract extraction to reduce inflammation and enhance visual and ocular recovery.

Diclofenac sodium, a NSAID, is a diphenylamine acetic acid derivative with anti-inflammatory, antipyretic and analgesic activity. In the oral dosage form, diclofenac sodium is available in more than 115 countries for use in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The topical ophthalmic formulation of diclofenac sodium, 0.1%, Voltaren Ophthalmic Solution, 0.1% (Voltaren) is indicated for treatment of inflammation following post-cataract surgery and photophobia in patients undergoing incisional refractive surgery. The anti-inflammatory pharmacological action of diclofenac sodium is attributed to its ability to inhibit cyclo-oxygenase, the committed enzyme step in the biosynthesis of prostaglandins, resulting in a significant reduction in prostaglandin levels (e.g., PGE_2). Diclofenac appears to decrease arachidonic acid bioavailability by shunting this substance to the triglyceride pool and may partially inhibit leukotriene production at high doses. Extensive preclinical pharmacology and toxicology studies of diclofenac sodium conducted by [redacted] and Alcon Laboratories, Inc., support the safety profile of the compound for topical ocular administration.

Voltaren is approved for treatment of anterior chamber inflammation following cataract surgery (NDA 20-037). Published clinical studies in 309 patients show that Voltaren treatment reduces post-surgical inflammation compared to placebo.

In this submission, Alcon will attempt to demonstrate the therapeutic equivalence of Alcon's proprietary Diclofenac Sodium Ophthalmic Solution, 0.1% (Diclofenac) to Ciba's marketed product, Voltaren Ophthalmic in control of anterior chamber inflammation after cataract surgery. Presented in this application are the results of a 370-patient controlled clinical study of Diclofenac Sodium Ophthalmic Solution, 0.1% v. Voltaren Ophthalmic Solution, 0.1% v. Placebo, given q.i.d. for two weeks after cataract surgery and a 20-patient, single-dose comfort study of Diclofenac Sodium Ophthalmic Solution, 0.1% v. Voltaren Ophthalmic Solution, 0.1%.

6.3 Foreign Experience

An oral dosage form of diclofenac sodium (Voltaren®) has been marketed by Ciba-Geigy in over 115 countries for treatment of various rheumatic and nonrheumatic conditions. A topical ophthalmic formulation containing diclofenac sodium, 0.1% (Voltaren Ophthalmic) is widely available, including Canada, the United States and Europe for the treatment of postoperative inflammation in patients who have undergone cataract extraction. More recently, CibaVision obtained approval in the U.S. for the additional indication of treatment of photophobia in patients undergoing incisional refractive surgery.

Diclofenac sodium ophthalmic solution, 0.1% has not been withdrawn from marketing in any country.

6.4 Human Pharmacology

Diclofenac sodium is the active ingredient in two approved NDAs: Voltaren Ophthalmic Solution, 0.1% (NDA 20-037) and Voltaren tablets (NDA 19-201). As such, the pharmacokinetics and dispositions of diclofenac in humans have been investigated and extensively reported in the literature.

Diclofenac sodium (Voltaren) is absorbed into the eye after topical ocular dosing. Aqueous humor concentrations range from 50 ng/mL following a single dose, to 130 ng/mL following multiple daily doses (1-4).

In comparison to oral dose regimens, systemic exposure is substantially lower after topical ocular dosing. In normal volunteers receiving either 2 drops or 3 to 16 drops of 0.1% diclofenac, plasma concentrations were found to be below the quantitation limit of the assays (< 5 to 10 ng/mL). In contrast, oral doses of 25 to 150 mg resulted in plasma concentrations of approximately 5000 to 3500 ng/mL.

7 Description of Clinical Data Sources

Diclofenac Sodium Ophthalmic Solution, 0.1%: Clinical Pharmacology and Controlled Efficacy Studies

Study Type	Protocol	Concentration	Dosing	Control	Duration	No. Patients
Clinical Pharmacology (Comfort)	C-95-16	0.1%	Single drop	Voltaren 0.1% (cross-over)	1 Day	20
Efficacy and Safety (Post-Cataract Inflammation)	C-95-07	0.1%	One drop, q.i.d.- 24 hours after cataract surgery	Voltaren 0.1%, Placebo Vehicle (Parallel Group)	14 Days	370

8 Clinical Studies

Study #1

8.1.1 Protocol # C-95-07

Title: Comparison of Diclofenac Sodium Ophthalmic Solution, 0.1% to Voltaren Ophthalmic Solution, 0.1% and to Placebo in Control of Post-Cataract Surgery Inflammation

Objectives:

The study objectives were to compare the safety and efficacy of Diclofenac to Voltaren and to placebo in the control of anterior chamber inflammation after cataract surgery by phacoemulsification (PHACO) or extracapsular (ECCE) method with implantation of a posterior chamber intraocular lens.

Study Design:

The study was a multi-center, randomized, triple-masked, placebo-controlled, three-arm, parallel group trial comparing efficacy and safety of Diclofenac to Voltaren and placebo in the control of anterior chamber inflammation in eyes of patients who have undergone cataract extraction by phacoemulsification or extracapsular extraction, with implantation of a posterior chamber lens.

The primary efficacy evaluations were based on clinical severity scores of anterior chamber cells (0-4 scale) and anterior chamber flare (0-4 scale). The secondary efficacy variables were treatment failures and visual acuity. All other clinical assessments (e.g., intraocular pressure) were considered safety variables. The dosing regimen was one drop q.i.d., administered to the operative eye beginning one day (22-34 hours) after cataract surgery and continuing for 14 days.

Three hundred seventy patients were randomized to treatment and evaluable for safety; 126 to Diclofenac 123 to Voltaren and 121 to placebo (Diclofenac vehicle).

Clinical assessments were performed at Study Days 1 (22-34 hours post surgery), 4 (+/- 1), 8 (+/- 1) and 15 (+/- 1).

At the discretion of the investigator, patients were treated postoperatively with topical antibiotics and if necessary, ocular hypotensive agents to control IOP postoperatively or during the course of the study. No other topical ocular, subconjunctival or systemic anti-inflammatory or analgesic drugs were allowed.

Study Population

Adult males and non-pregnant females who underwent cataract extraction with implantation of an intraocular lens and who had a summed score of at least 4 units in the baseline evaluation of cells and flare (at least two of which were flare), one day (22-34 hours) after cataract extraction.

Endpoints

The **primary efficacy evaluations** were based upon clinical severity scores of anterior chamber flare and anterior chamber cells. The severity of cells and flare was scored and recorded as outlined below.

Aqueous Cells	Aqueous Flare
0- None	0- Absent
1- 1-5 cells	1 - Trace
2 - 6-15 cells	2 - Mild intensity
3 - 16-30 cells	3 - Moderate intensity
4 - Greater than 30 cells	4 - Severe intensity

The **secondary efficacy variables** are treatment failures and visual acuity. All other clinical assessments were considered to be safety variables.

Treatment failure was defined as the presence of a summed score of anterior chamber cells and flare equal to or greater than the patient's baseline score (22-34 hours postop). To be considered evaluable per protocol, a patient had to: meet inclusion/exclusion criteria, receive drug, and return for follow-up visits or be judged as a treatment failure.

Anterior chamber response was quantitated by the observer under dim room illumination. The slit-lamp specifications were as follows: narrowest slit beam of 0.5 mm width and a least 8 mm in length, an examination angle of approximately 45 degrees and a magnification of 16X. The number of cells in the anterior chamber was determined as the average of three counts of ten seconds each. Flare was determined using the same slit-lamp specifications as for cells.

At each center, the observer designated to perform the clinical assessments of inflammation and the overall assessments of the inflammatory response was the same for all patients throughout the duration of the study.

Reviewer's Comments: *There is no mention as to whether the surgeon was allowed to be the designated observer. If the surgeon were the observer, this could introduce bias into the observations.*

Statistical Considerations

Both the intent-to-treat and the per protocol data sets were used in the analysis of the primary efficacy variables; aqueous cells and flare. P-values from the analysis of variance results for treatment comparisons between Diclofenac and placebo and Voltaren and placebo were used to evaluate the efficacy of the active treatments compared to placebo. A p-value of less than $\alpha = 0.05$ was considered supportive of a significant treatment effect.

Evaluation of equivalence of Diclofenac and Voltaren was based on confidence intervals for the difference between Diclofenac and Voltaren at each visit. Specifically, if the 95% confidence interval about the observed treatment differences between Diclofenac and Voltaren for both aqueous cells and flare falls within the interval (-0.8,0.8), equivalence between Diclofenac and Voltaren was declared.

Reviewer's Comments:

A difference of 1-unit from placebo has been considered the minimum difference for showing a clinically significant treatment effect when comparing the active treatment to placebo.

Safety Parameters

Safety parameters for this study included measuring change from baseline of intraocular pressure, visual acuity, and any signs of clinical worsening of the dilated fundus examination. Intraocular pressure and visual acuity were measured at each visit and a dilated fundus examination was performed at the Screening Exam and at the end of the study.

Investigators:

Inv. #		#Enrolled	#Completed
1300	Kerry Assil, M.D. Sinskey Institute 2232 Santa Monica Boulevard Santa Monica, CA 90411	20	15
847	Stephen F. Brint, M.D. Eye Surgery Center 5640 Read Boulevard New Orleans, LA 70127	12	9
1208	Robert Caine, M.D. Eye Associates of Virginia 110 Cambridge Street Fredericksburg, VA 22405	7	5
362	Delmar R. Caldwell, M.D. Department of Ophthalmology Tulane University Medical Center 1430 Tulane Avenue New Orleans, LA 70112	11	7
1229	James L. Crabb, M.D. Eye Tech 5406 Knight Arnold Avenue Memphis, TN 78229	52	49
501	Mitchell H. Friedlaender, M.D. Scripps Clinic 10666 North Torrey Pines Road La Jolla, CA 92037	5	5

1832	John D. Goosey, M.D. Houston Eye Associates 2855 Gramercy Houston, TX 77025	21	19
1008	Barry Horwitz, M.D. Horwitz & Whitsett, P.C. 8945 Long Point Road, Suite 111 Houston, TX 77025	13	10
1499	Mark S. Jaffe, M.D. Jaffe Eye Institute 18999 Biscayne Boulevard North Miami Beach, FL 33180	30	23
695	Manus Kraff, M.D. Kraff Eye Institute 5600 W. Addison Street, 4th Floor Chicago, Illinois 60634	10	7
970	Robert P. Lehmann, M.D. Lehmann Eye Center 5300 North Street Nacogdoches, TX 75961	52	45
498	James P. McCulley, M.D. Department of Ophthalmology Univ. Texas Southwest Med. Center 5323 Harry Hines Boulevard Dallas, TX 75235	9	9

1403	Jeffrey B. Morris, M.D. North Coast Eye Center 3909 Waring Road, Suite B Oceanside, CA 92056	27	21
750	Kenneth W. Olander, M.D., Ph.D. Eye Physician Associates S.C. 2901 W. KK River Parkway, Suite 170 Milwaukee, WI 53215	22	17
225	Robert Poirer, M.D. South Texas Family Eye Center 7810 South Pasteur Street San Antonio, TX 78229	3	1
1806	Kenneth Sall, M.D. Bellflower Medical Center 9604 East Artesia Boulevard, Suite 203 Bellflower, CA 90706	36	31
271	Robert Stewart, M.D. Houston Eye Associates 2855 Gramercy Houston, TX 77025	39	36
1964	Ramesh C. Tripathi, M.D., Ph.D. South Carolina Eye Institute 4 Richland Medical Park, Suite 300 Columbia, SC 29203	1	0

Results
Populations enrolled/analyzed

Demographics for Intent to Treat Patients

Sex

TRT	Male N	Male %	Female N	Female %
Diclofenac	44	35	82	65
Voltaren	41	33	82	67
Placebo	44	36	77	64
Total	129	35	241	65

Race

TRT	Caucasian N	Caucasian %	Black N	Black %	Asian N	Asian %	Other N	Other %
Diclofenac	87	69	26	21	3	2	10	8
Voltaren	87	71	26	21	2	2	8	7
Placebo	83	69	26	21	3	2	9	7
Total	257	69	78	21	8	2	27	7

Iris

TRT	Brown N	Brown %	Hazel N	Hazel %	Green N	Green %	Blue N	Blue %	Grey N	Grey %
Diclofenac	74	59	13	10	7	6	30	24	2	2
Voltaren	69	56	11	9	4	3	37	30	2	2
Placebo	66	55	7	6	6	5	41	34	1	1
Total	209	56	31	8	17	5	108	29	5	1

Age

TRT	Mean	Std	N	Min	Max
Diclofenac	72.4	8.22	126	39	94
Voltaren	72.4	9.09	123	44	99
Placebo	70.8	9.89	121	41	88
Total	71.9	9.09	370	39	99

Age Category

TRT	12-<65 N	12-<65 %	>= 65 N	>= 65 %
Diclofenac	17	13	109	87
Voltaren	18	15	105	85
Placebo	23	19	98	81
Total	58	16	312	84

Type of Surgery	Diclofenac	Voltaren	Placebo	Total
ECCE	20	20	18	58
PHACO	105	105	103	311

Distribution of Enrolled Patients by Treatment and Investigator

INV	Total N	TRT Diclofenac N	%	Voltaren N	%	Placebo N	%
225	3	1	33	1	33	1	33
271	39	13	33	13	33	13	33
362	11	4	36	4	36	3	27
498	9	3	33	3	33	3	33
501	5	2	40	1	20	2	40
695	10	3	30	4	40	3	30
750	22	7	32	8	36	7	32
847	12	4	33	4	33	4	33
970	52	18	35	17	33	17	33
1008	13	4	31	5	38	4	31
1208	7	3	43	2	29	2	29
1229	52	18	35	17	33	17	33
1300	20	7	35	6	30	7	35
1403	27	9	33	9	33	9	33
1499	30	10	33	10	33	10	33
1806	36	12	33	12	33	12	33
1832	21	7	33	7	33	7	33
1964	1	1	100	.	.	.	.
Total	370	126		123		121	

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Disposition of Patients:

	Number of Patients			
	Diclofenac	Voltaren	Placebo	Total
Enrolled	126	123	121	370
Randomized	126	123	121	370
Completed Study	109	115	85	309
Discontinued Prematurely	17	8	36	61
Adverse Event	8	4	19	31
Treatment Failure	1	1	13	15
Lost to Follow Up	3	2	2	7
Patient Decision	4	0	2	7
Use of Unacceptable Medication	1	1	0	2
Evaluated for Efficacy	120	117	115	352
Evaluated for Safety	126	123	121	370

Patients Who Were Not Evaluable

INV	PAT	Treatment	Reason Not Evaluable
498	7006	Diclofenac	Contraindicated meds (Solu-medrol and Maxitrol pre-op)
501	3002	Diclofenac	Contraindicated meds (Ocufen pre-op and Tobradex post-op)
501	3004	Diclofenac	Contraindicated meds (Ocufen pre-op and Tobradex post-op)
1403	1401	Diclofenac	Contraindicated meds (NSAID use in contralateral non-op eye)
1403	1410	Diclofenac	Lost to follow-up (no post-treatment efficacy data)
1964	8001	Diclofenac	Contraindicated meds (Ocufen pre-op)
271	409	Placebo	Lost to follow-up (no post-treatment efficacy data)
271	427	Placebo	Contraindicated meds (Lodine used throughout study)
498	7002	Placebo	Exclusion #1 (Surgical Complication - iris prolapse)
498	7004	Placebo	Contraindicated meds (Maxitrol post-op)
501	3001	Placebo	Contraindicated meds (Ocufen pre-op and Tobradex post-op)
501	3005	Placebo	Contraindicated meds (Ocufen pre-op and Tobradex post-op)
498	7008	Voltaren	Contraindicated meds (Fluorbiprofen use pre-op)
501	3003	Voltaren	Contraindicated meds (Ocufen pre-op and Tobradex post-op)
1008	304	Voltaren	Contraindicated meds (FML used in non-study eye)
1300	813	Voltaren	Contraindicated meds (Ocular/systemic steroid use)
1403	1418	Voltaren	Lost to follow-up (no post-treatment efficacy data)
1403	1424	Voltaren	Insufficient cell and flare score at Baseline

Efficacy Endpoint Outcomes

Primary Efficacy Parameters for Per Protocol Patients

Sg/Sx	Trt		Visit			
			Base	Day 4	Day 8	Day 15
Cells	Diclofenac	Mean	2.8	2.3	1.9	1.2
		std	0.827	1.131	1.253	1.232
		n	120	118	116	106
	Voltaren	Mean	2.7	2.2	1.7	1.0
		std	0.835	1.196	1.200	1.035
		n	117	115	113	111
	Placebo	Mean	2.7	2.4	2.2	2.0
		std	0.833	1.151	1.216	1.260
		n	115	114	103	93
		p-val(V-D)*	0.53	0.75	0.41	0.24
		p-val(D-P)*	0.47	0.34	0.04	<.01
		p-val(V-P)*	0.93	0.21	<.01	<.01
Flare	Diclofenac	Mean	2.3	1.5	1.1	0.7
		std	0.568	0.940	0.965	0.805
		n	120	118	116	106
	Voltaren	Mean	2.3	1.5	1.0	0.6
		std	0.549	0.949	0.921	0.767
		n	117	115	113	111
	Placebo	Mean	2.3	1.9	1.7	1.4
		std	0.441	1.033	1.102	1.090
		n	115	114	103	93
		p-val(V-D)*	0.88	0.63	0.46	0.30
		p-val(D-P)*	0.57	<.01	<.01	<.01
		p-val(V-P)*	0.68	<.01	<.01	<.01

*ANOVA

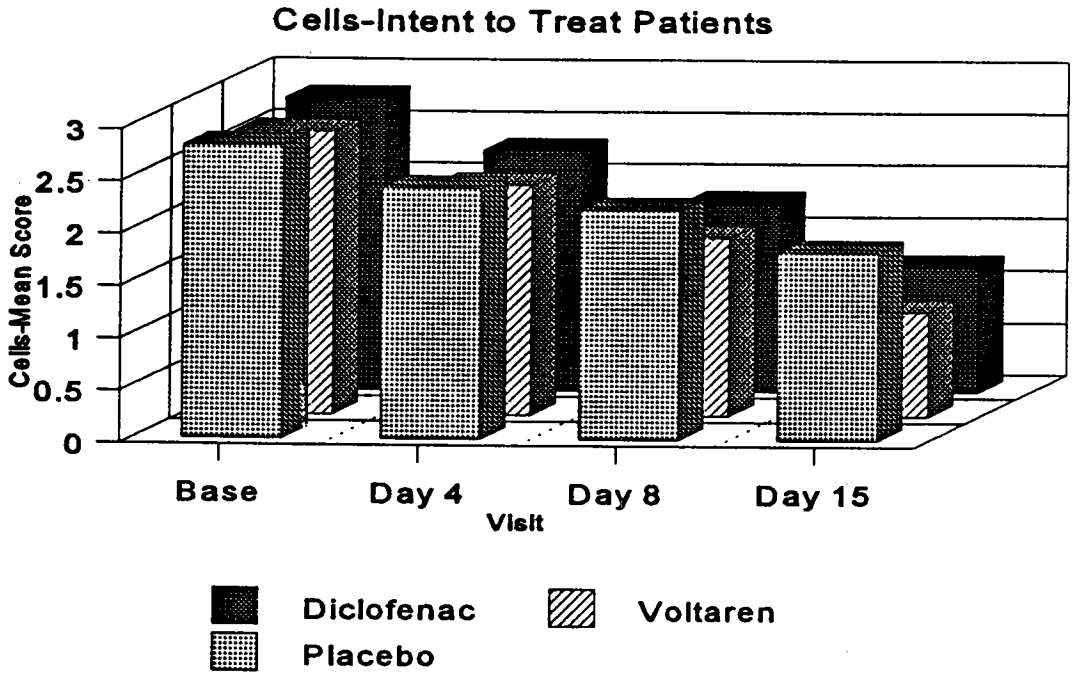
Reviewer's Comments: *The data demonstrate that Diclofenac does not achieve 1-unit of superiority over placebo with respect to cells or flare at any visit. A minimum of 1-unit of superiority over placebo has been the standard required to claim clinical efficacy. The comparitor, Voltaren, meets the 1-unit of superiority over placebo for cells on Day 15. The comparison between Diclofenac and Voltaren, with respect to cells on Day 15, represents a 20% difference in resolution of one of the primary indicators of postoperative cataract inflammation.*

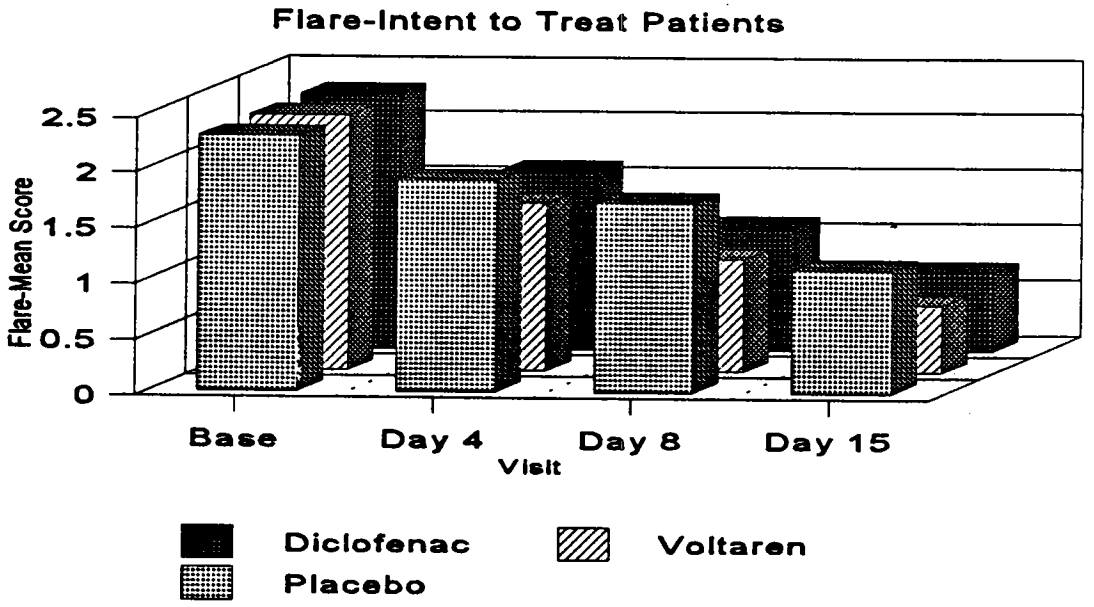
Primary Efficacy Parameters for Intent to Treat Patients

Sg/Sx	Trt		Visit Base	Day 4	Day 8	Day 15
Cells	Diclofenac	Mean	2.8	2.3	1.8	1.2
		std	0.824	1.133	1.255	1.221
		n	125	122	119	109
	Voltaren	Mean	2.7	2.2	1.7	1.0
		std	0.850	1.193	1.216	0.991
		n	123	120	118	115
	Placebo	Mean	2.8	2.4	2.2	1.8
		std	0.847	1.169	1.222	1.196
		n	121	119	106	85
		p-val(D-V)*	0.51	0.62	0.37	0.18
		p-val(D-P)*	0.65	0.30	0.02	<.01
		p-val(V-P)*	0.84	0.13	<.01	<.01
Flare	Diclofenac	Mean	2.3	1.6	1.1	0.7
		std	0.567	0.963	0.945	0.780
		n	125	122	119	109
	Voltaren	Mean	2.3	1.5	1.0	0.6
		std	0.545	0.952	0.933	0.727
		n	123	120	118	115
	Placebo	Mean	2.3	1.9	1.7	1.1
		std	0.443	1.041	1.085	0.854
		n	121	119	106	85
		p-val(D-V)*	0.80	0.43	0.51	0.26
		p-val(D-P)*	0.50	<.01	<.01	<.01
		p-val(V-P)*	0.68	<.01	<.01	<.01

*ANOVA

Reviewer's Comments: *The data above, again, demonstrate that although Diclofenac is statistically significantly superior to placebo, it does not reach the minimum of 1-unit of superiority over placebo, which is required to claim clinical efficacy.*

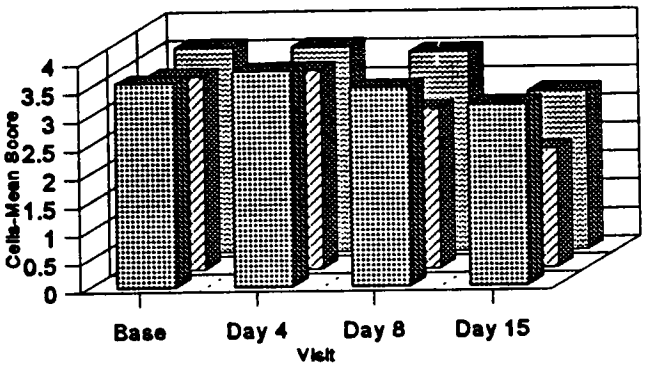




Reviewer's Comments: *When the mean scores for cell and flare are plotted in bar-graph form, as above, it is clear that Diclofenac does not show the minimum of 1-unit of superiority over placebo at any of the visits for either cell or flare. (Data taken from Table 11, pg.8-0215 of sponsor's submission)*

Primary Efficacy Parameters for Intent to Treat Patients by Investigator-CELLS

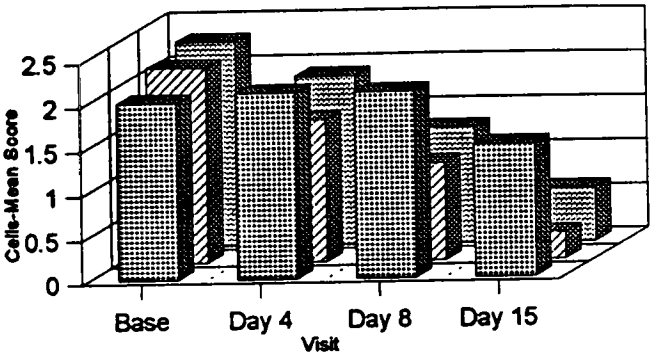
Cells-Intent to Treat Patients-INV#271



36 patients

Diclofenac Voltaren
Placebo

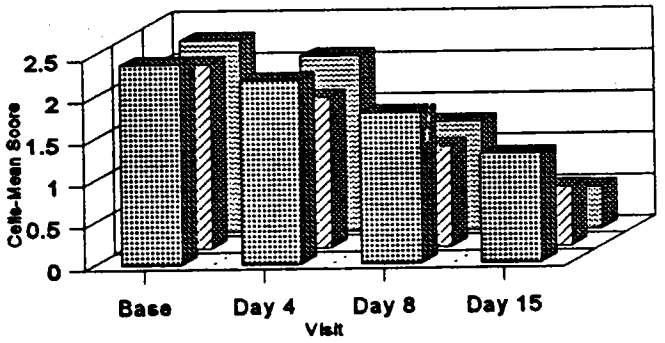
Cells-Intent to Treat Patients-INV#970



45 patients

Diclofenac Voltaren
Placebo

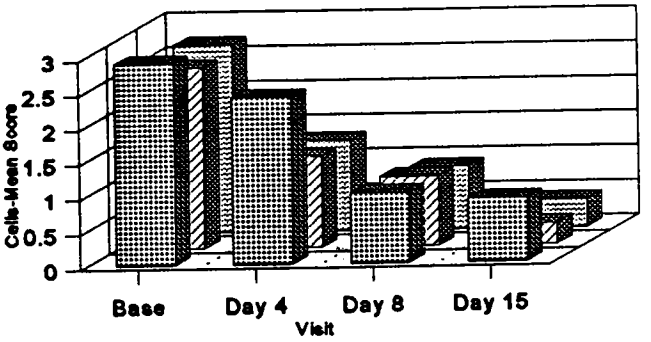
Cells-Intent to Treat Patients-INV#1229



49 patients

Diclofenac Voltaren
Placebo

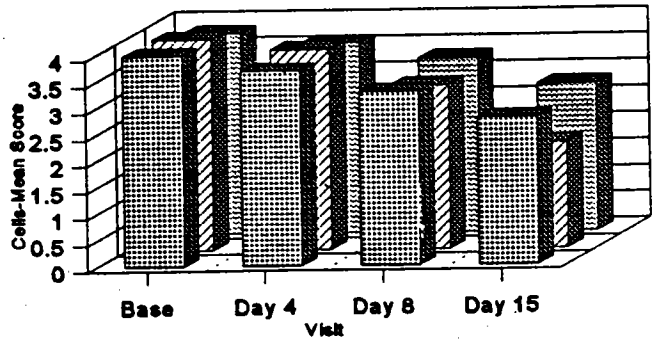
Cells-Intent to Treat Patients-INV#1499



23 patients

Diclofenac Voltaren
Placebo

Cells-Intent to Treat Patients-INV#1806



31 patients

Diclofenac Voltaren

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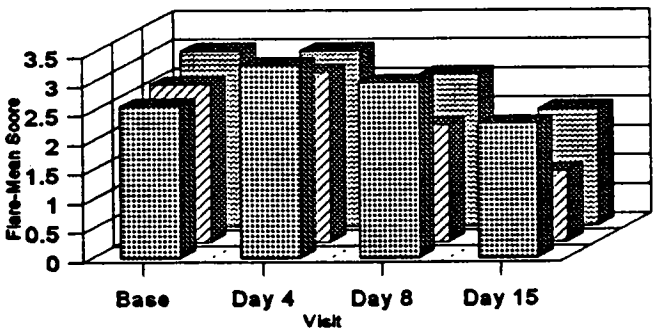
Primary Efficacy Parameters for Intent to Treat Patients by Investigator-FLARE

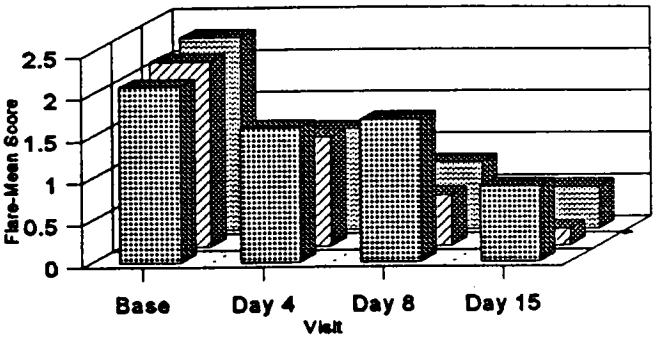
Flare-Intent to Treat Patients-INV#271



36 patients

Diclofenac Voltaren
Placebo

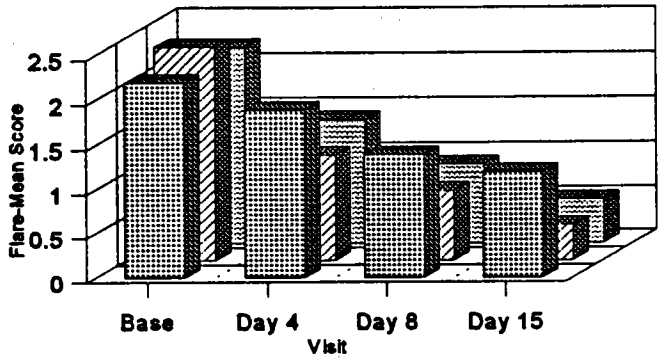
Flare-Intent to Treat Patients-INV#970



45 patients

Diclofenac Voltaren
Placebo

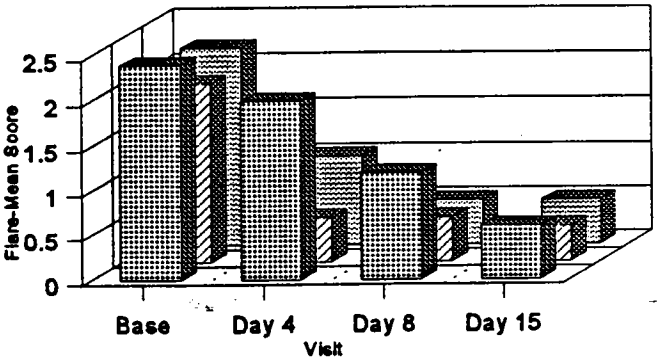
Flare-Intent to Treat Patients-INV#1229



49 patients

Diclofenac Voltaren
Placebo

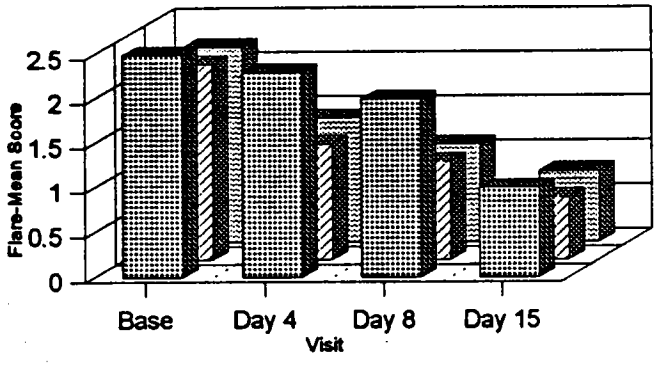
Flare-Intent to Treat Patients-INV#1499



23 patients

Diclofenac Voltaren
Placebo

Flare-Intent to Treat Patients-INV#1806

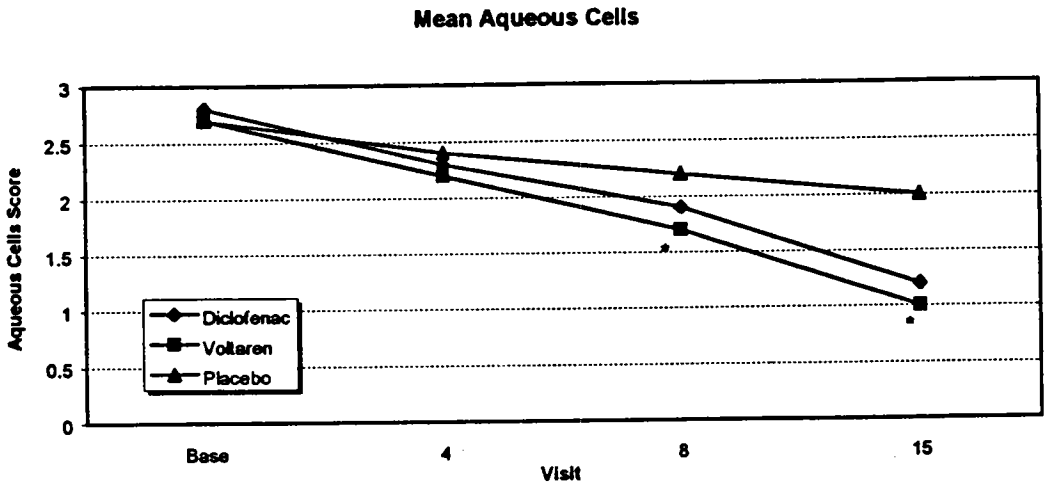


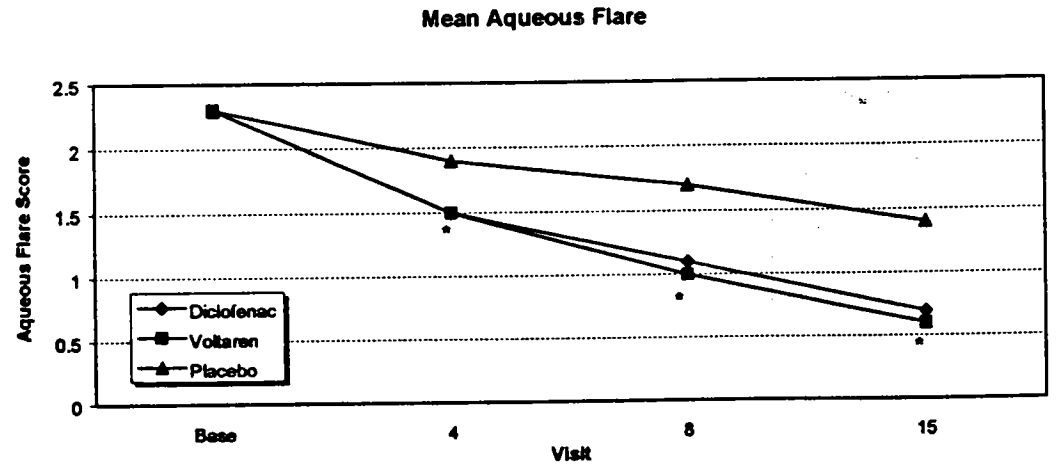
31 patients

Diclofenac Voltaren

APPEARS THIS WAY
ON ORIGINAL

Reviewer's Comments: *The preceding bar-graphs show concurrence among the five major centers in this study, namely, that Diclofenac consistently performs below the minimum standard for clinical efficacy of 1-unit of superiority over placebo for both cells and flare. (Data for graphs taken from Table 12, pgs.8-0216-8-0223 of sponsor's submission)*





Reviewer's Comments: *This graph was taken directly from the sponsor's NDA submission. Although Diclofenac is statistically superior to placebo, it fails to meet the 1-unit standard of superiority over placebo with respect to cells and flare necessary to claim clinical efficacy. The comparator, Voltaren, meets the 1-unit of superiority over placebo with respect to cells on Day 15.*

Secondary Efficacy Parameters

Treatment Failures:

	Number	Percent
Diclofenac	**1/120**	**<1**
Voltaren	**1/117**	**<1**
Placebo	**13/115**	**11**

Reviewer's Comments: *There is no clinically significant difference in the treatment failure rate of Diclofenac compared to Voltaren. Both Diclofenac and Voltaren were statistically and clinically superior to placebo for treatment failure rate. Results for intent-to-treat were supportive of per protocol results.*

Safety Outcomes:

Frequency and Incidence of Adverse Events

Coded Adverse Events	Diclofenac 0.1% Ophthalmic Solution N=126		Voltaren 0.1% Ophthalmic Solution N=123		Placebo (Diclofenac Ophthalmic Vehicle) N=121	
	N	%	N	%	N	%
Ocular						
Discomfort	5	4	11	10	4	3
Pruritus	5	4	6	5	9	7
Hyperemia	5	4	5	4	23	19
Tearing	4	3	1	<1	8	7
Follicular Conjunctivitis	3	2	3	2	0	
Discharge Eye NOS	3	2	0		2	2
Keratitis	2	2	6	5	1	<1
Conjunctival Discharge	2	2	0		1	<1
Conjunctival Edema	1	<1	1	<1	2	2
Increased IOP	1	<1	3	2	0	
Pain	1	<1	1	<1	11	9
Eye Edema	0		1	<1	1	<1
Keratopathy	0		2	2	0	
Foreign Body Sensation	1	<1	3	2	13	11
Photophobia	0	<1	0		9	7
Allergic Reaction	0		0		1	<1
Cells	0		0		1	<1
Conjunctivitis	1	<1	0		1	<1

Coded Adverse Events	Diclofenac 0.1% Ophthalmic Solution N=126		Voltaren 0.1% Ophthalmic Solution N =123		Placebo (Diclofenac Ophthalmic Vehicle) N=121	
Lid Edema	1	<1	1	<1	1	<1
Flare	0		0		1	<1
Abnormal Vision	0		0		1	<1
Blurred Vision	1	<1	2	2	4	3
Iritis	2	2	0		4	3
Blepharitis	2	2	0		0	
Eye Disorder	2	2	0		0	
Dry Eye	1	<1	0		1	<1
Corneal Abrasion	1	<1	0		0	
Lid Margin Discharge	1	<1	0		0	
Infection	1	<1	0		0	
Lacrimation Disorder	1	<1	0		0	
Lid Spasm	1	<1	0		0	
Ulcer Conjunctival	1	<1	0		0	
Vitreous Disorder	0		3	2	0	
Corneal Edema	0		1	<1	2	2
Macular Edema	0		1	<1	1	<1
Glaucoma	0		1	<1	1	<1
Keratopathy	0		1	<1	1	<1
Surgical/Medical Procedure	0		1	<1	1	<1
Lid Erythema	0		1	<1	0	
Fatigue	0		1	<1	0	

Lid Margin Crusting	0		1	<1	0	
Retinal Disorder	0		1	<1	0	
Sticky Sensation	0		1	<1	0	
Uveitis	2	2	0		3	3
Edema Periorbital	0		0		1	<1
Hyphema	0		0		1	<1
Irritation	0		0		1	<1
Corneal Ulcer	0		0		1	<1
Nonocular						
Metabolic and Nutritional Abnormal Healing	0		1	<1	0	
Nervous System Hyperesthesia Nervousness	0 1	<1	0 0		1 0	<1
Body As A Whole Asthenia	1	<1	0		0	
Cold Syndrome	1	<1	0		0	
Headache	0		0		1	<1
Cardiovascular Supraventricular Tachycardia	1	<1	0		0	
Digestive System Colitis	1	<1	0		0	
Hemic and Lymphatic System Increased Fibrin	0		0		2	2
Respiratory System Increased Cough	1	<1	0		0	

Rhinitis	1	<1	0		0	
Bronchitis	0		1	<1	0	
Hemoptysis	0		1	<1	0	
Skin and Appendages Sweat	1	<1	0		0	
Pruritus	0		0		1	<1
Urogenital System Urinary Tract Infection	2	2	0		0	

Reviewer's Comments: *In general, there were fewer adverse events and a lower incidence of them in the Diclofenac and Voltaren groups than in the placebo group. The most frequently reported adverse events in the Diclofenac and Voltaren groups were discomfort, pruritus, hyperemia and tearing. There were no reports of serious side effects in any of the three groups.*

Visual Acuity

Change in Visual Acuity (Snellen Lines)										
Treatment	Improved		No Change		1 Line Decrease		2 Lines Decrease		>2 Line Decrease	
	N	%	N	%	N	%	N	%	N	%
Diclofenac N=126	93	78%	19	16%	3	3%	4	3%	1	<1%
Voltaren N=123	94	80%	16	14%	5	4%	1	1%	1	<1%
Placebo N=121	57	50%	26	23%	19	17%	4	4%	9	8%

Reviewer's Comments: *Diclofenac and Voltaren had statistically and clinically less worsening from baseline visual acuity than placebo.*

Intraocular Pressure

Summary Statistics for IOP (Change from Baseline)

			Change from Baseline		
		BASELINE	DAY 4	DAY 8	DAY 15
Diclofenac	Mean	16.58	-0.21	-0.02	-1.57
	STD	5.88	5.09	6.23	5.47
	N	124	121	118	108
	MIN	2.00	-18.00	-18.00	-28.00
	MAX	48.00	16.00	19.00	9.00
Percent of Patients with IOP increase ≥ 10mm Hg			3%	6%	0%
Voltaren	Mean	16.41	-0.53	0.04	-0.41
	STD	5.51	5.43	5.70	4.96
	N	123	120	118	115
	MIN	2.00	-15.00	-17.00	-12.00
	MAX	40.00	34.00	20.00	27.00
Percent of Patients with IOP increase ≥ 10mm Hg			2%	3%	1%
Placebo	Mean	16.47	-1.66	-1.05	-0.96
	STD	5.31	4.21	4.56	4.94
	N	121	119	106	85
	MIN	0.00	-13.00	-15.00	-13.00
	MAX	32.00	8.00	9.00	12.00
Percent of Patients with IOP increase ≥ 10mm Hg			0.0%	0.0%	2%

Reviewer's Comments: *There are no clinically or statistically significant differences in intraocular pressure increase between the three groups. At baseline, there were essentially equivalent numbers of patients being treated concomitantly for glaucoma in the three groups (Diclofenac-10 pts.; Placebo-12 pts.; Voltaren-8 pts.). There were, however, almost twice as many patients begun on glaucoma medications for elevated intraocular pressure in the Diclofenac group (10) and the Voltaren group (8), as compared to the placebo group (5). There was no bias introduced with respect to investigator in this regard.*

Dilated Fundus Examination

Change from Screening Visit in Retina, Macula, Choroid Score

	Missing		Better/No Change		Worsened		ALL
Treatment	N	%	N	%	N	%	N
Diclofenac	15	12	110	87	1	<1	126
Voltaren	6	5	116	94	1	<1	123
Placebo	30	25	91	75	.	.	121

Change from Screening Visit in Optic Nerve Score

	Missing		Better/No Change		Worsened		ALL
Treatment	N	%	N	%	N	%	N
Diclofenac	15	12	111	88	.	.	126
Voltaren	6	5	116	94	1	<1	123
Placebo	30	25	91	75	.	.	121

Change from Screening Visit in Disc Pallor

	Missing		Better/No Change		ALL
	N	%	N	%	N
Diclofenac	16	13	110	87	126
Voltaren	6	5	117	95	123
Placebo	30	25	91	75	121

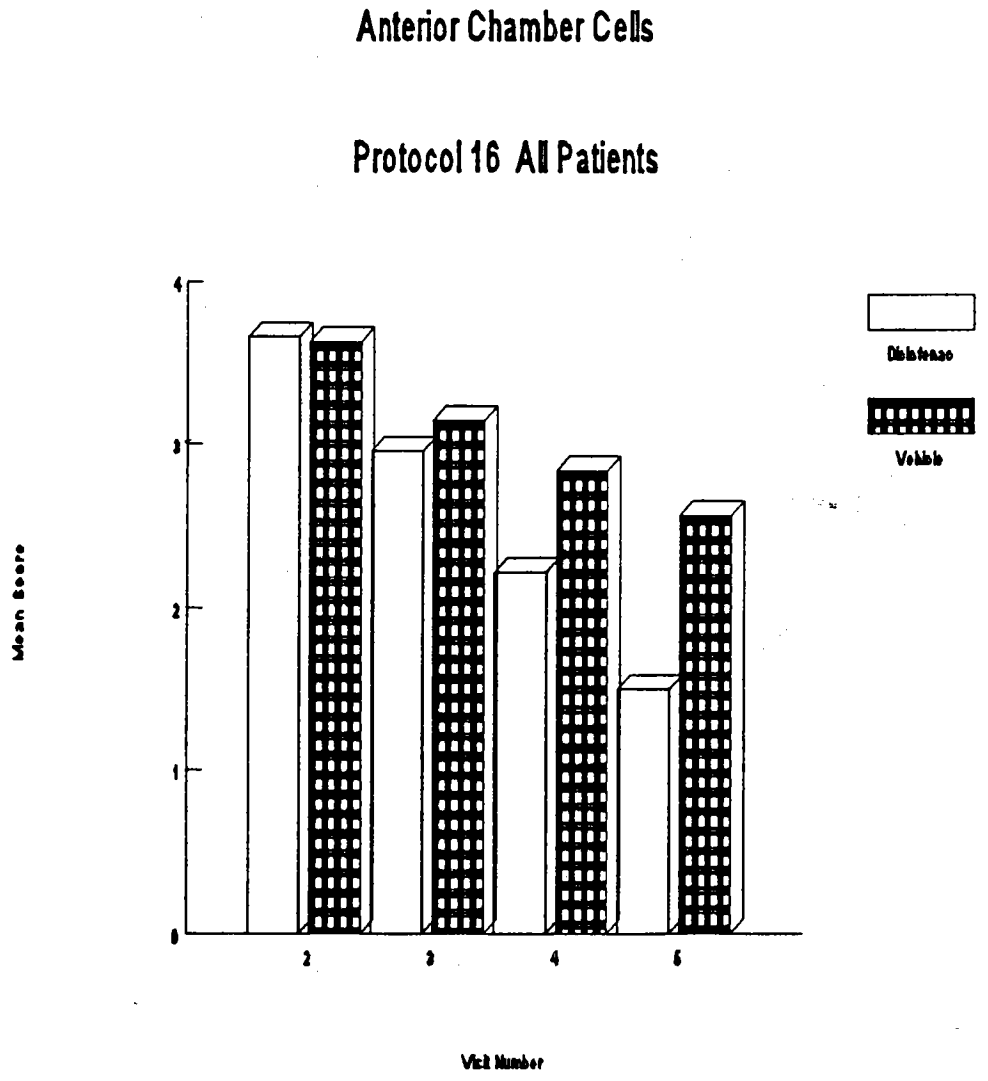
Change from Screening Visit in Cup to Disk Ratio

Treatment		Screening	Final Fundus Exam
Diclofenac	Mean	0.33	-0.01
	STD	0.14	0.06
	N	126	123
Voltaren	Mean	0.34	-0.01
	STD	0.14	0.06
	N	121	121
Placebo	Mean	0.34	0.00
	STD	0.15	0.03
	N	117	114

Reviewer's Comments: *There are no clinically or statistically significant differences between the three study groups with respect to dilated fundus examination. There are, however, a relatively large number of patients with missing values, particularly in the Diclofenac and placebo groups.*

Reviewer's Conclusions Regarding Efficacy Study # 1

The purpose of Study C-95-07 was to show clinical equivalence of Diclofenac and Voltaren in the treatment of anterior chamber inflammation after cataract extraction. Not only did Diclofenac perform less well than Voltaren in this study, it did not achieve the minimum standard of 1-unit of superiority over placebo required to demonstrate clinical efficacy. Voltaren achieved the 1-unit of superiority over placebo in this study compared to Diclofenac's performance of 0.8 units of superiority over placebo. This represents a 20% difference between the two drugs. Voltaren's initial approval (NDA-037) was based on scores just above the 1-unit over placebo needed to demonstrate clinical efficacy, as can be seen in the bar graph below. (Graph is from original medical review of NDA 20-037, 7/25/90, for which approval was granted)



Visit 3=Days 3-5; Visit 4=Days 7-9; Visit 5=Days 14-16

Reviewer's Conclusions Regarding Safety Study # 1

With respect to safety, Diclofenac and Voltaren had essentially the same profiles with respect to adverse events, except for discomfort which was greater in the Voltaren group, and tearing which was greater in the Diclofenac group. The most commonly reported adverse events for the two active groups were ocular discomfort, pruritus, hyperemia and tearing. The placebo group had a higher incidence and greater frequency of adverse events when compared to the Diclofenac and Voltaren groups.

Of significance, is that there were almost twice as many patients started on medication for treatment of elevated IOP in the Diclofenac and Voltaren groups as compared to the placebo group.