Study # 2

Protocol C-95-16

Title: Single Dose Comfort and Safety Evaluation of Diclofenac Sodium Ophthalmic Solution, 0.1% Compared to Voltaren Ophthalmic Solution, 0.1%

Objective/Rationale:

The study objective was to assess ocular comfort and safety after topical installation of a single drop of Diclofenac or Voltaren in normal, healthy eyes.

Design:

This Phase 1 comfort study was a single-center, randomized, double-masked, two-period, cross-over study in 20 healthy, adult volunteers with a normal comprehensive ophthalmic examination. Subjects who met the inclusion and exclusion criteria were assigned randomly to one of two treatment order groups and received one drop of Diclofenac or Voltaren in the nondominant eye with a minimum 24-hour washout period between treatments.

Protocol

Population:

Healthy adults with a normal comprehensive ophthalmic examination. All subjects enrolled into the study must have a corrected visual acuity of 20/50 or better in each eye, no evidence of any acute, subacute, or chronic pathological ophthalmic condition and must not be using any routine ocular medications (OTC or prescription).

Study Plan:

PROCEDURES	Screening	Baseline Exam Visit	Period I Treatment Visit	Period II Treatment Visit	Exit Exam Visit
Identify Potential Subjects	X				
Contraindications	X				
Instruction on Use of Scales	X				
Informed Consent	X				
Visual Acuity		X			X
Slit-Lamp		X			X
Pregnancy Tests (Female Subjects)		X			X
Baseline Psychometric Scales			X		
Test Solutions Instilled			X	X	
Psychometric Scales			X	X	
Complete Exit Form					X
Dismiss Patient					X

Investigators:

Inv. No.	Name/Address	# Enrolled	# Completed
703	Clifton H. Beasley, Jr., M.D. Alcon In-House Clinic 6201 South Freeway Fort Worth, TX 76134	20	20

Endpoints: Comfort will be based on the following:

Ocular Discomfort Composite (0 to 250) which is a composite of individual scales rating from 0 to 50 each for burning, stinging, tearing, general discomfort and acceptability.

Membrane Discomfort Composite (0 to 150) which is a composite of individual scales rating from 0 to 50 each for foreign body sensation, lid sensation and dryness.

Visual Clarity (0 to 50)

Three-minute Burning profile

The evaluations will be done at Baseline (excluding the 3-minute burning profile) and immediately after instillation of the test article at each period.

Statistical Considerations:

This was a randomized, double-masked, single-center, two-period crossover study to assess ocular comfort of Diclofenac and Voltaren. Twenty (20) normal, healthy volunteers were enrolled in this study. Subjects were assigned randomly to one of the two treatment orders. One drop of each test medication was applied topically to the nondominant eye of each subject. A minimum 24 hours of washout between treatments was used.

All hypothesis tests were conducted with a 0.05 probability of a type 1 error. Summary statistics were provided for each of the variables in the analysis. The following comfort variables were used in the analysis:

Comfort Variable	Scale
Ocular Discomfort Composite (sum of Burning, Stinging, Discomfort, Tearing and Acceptability)	0 = None to 250 = Extreme
Membrane Discomfort Composite (sum of Foreign Body Sensation, Lid Sensation and Dryness)	0 = None to 150 = Extreme
Visual Clarity	0 = None to 50 = Poor
Burning Profile	0 = None to 50 = Extreme

Results

Populations enrolled/analyzed:

Demographics

Age

MEAN	STD	N	MIN	MAX
39.70	6.04	20	28.00	55.00

Age Category

0-<13		13-64		>=65	
N	%	N	%	N	%
0	0	20	100	0	0

Sex

Male		Female	
N	%	N	%
8	40	12	60

Race

Caucasian

N	%
20	100

Iris Color

Brown		Hazel		Green		Blue	
N	%	N	%	N	%	N	%
6	30	3	15	4	20	7	35

Disposition of Patients:

Number of patients completing each treatment period

(C9516: Intent-to-treat data set)

	Treatment period	
	Diclofenac	Voltaren
AVAILABLE	20	20
DISCONTINUED	0	0
TOTAL	20	20

All twenty (20) subjects received drug and completed the study according to the protocol. All subjects also met the inclusion/exclusion criteria.

Reviewer's Comment: *The data above are actually the "per protocol" data, as all 20 subjects completed the study according to the protocol. (Table taken directly from sponsor's submission, Vol.11-pg.8-0024)*

Endpoint Outcomes:

Ocular Discomfort Composite

Ocular discomfort is the sum of 5 individual symptoms (burning, stinging, tearing, general discomfort, and acceptability) scored on a scale of 0 to 50. Hence, ocular discomfort ranges from _____ A treatment difference of 10% of scale range _____ is considered clinically relevant. Results for ocular discomfort are summarized in the following table.

Ocular discomfort composite

	MEAN	STD	N
Diclofenac	15.65	16.86	20
Voltaren	33.85	41.05	20
Treatment Difference	-18.20		20
Upper 95% Conf. Limit	2.84		

Reviewer's Comment: *There are no clinically significant differences in ocular discomfort.*

Membrane Discomfort Composite

Membrane discomfort is the sum of 3 symptoms (body sensation, lid sensation, and dryness) scored on a scale of 0 to 50. Thus, membrane discomfort ranges _____ In this scale, a treatment difference of 10% of scale range _____ is considered clinically relevant. The following table summarize the results for membrane discomfort.

Membrane discomfort composite

	MEAN	STD	N
Diclofenac	5.25	10.36	20
Voltaren	4.85	6.73	20
Treatment Difference	0.40		20
Upper 95% Conf. Limit	3.40		

Reviewer's Comments: *There are no clinically significant differences in membrane discomfort.*

Visual Clarity

Visual clarity is scored on a scale ranging from In this scale, a treatment difference of 10% of scale range is considered clinically relevant. The following table summarize the results for visual clarity.

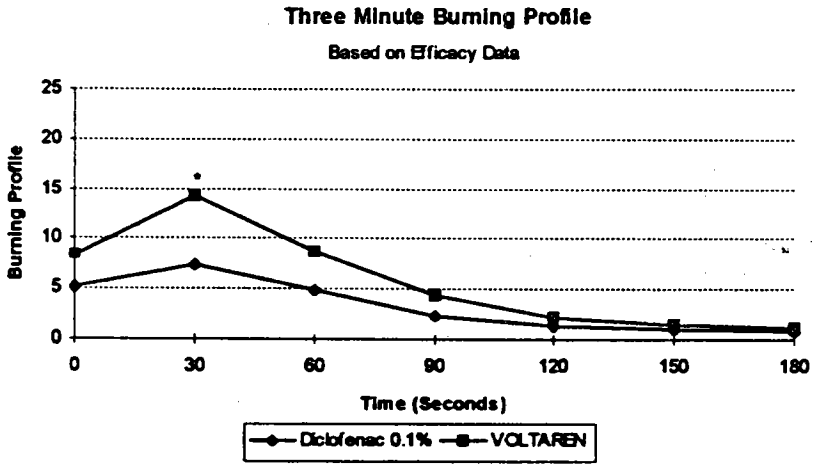
Visual Clarity

	MEAN	STD	N
Diclofenac	2.75	3.91	20
Voltaren	4.15	6.18	20
Treatment Difference	-1.40		20
Upper 95% Conf. Limit	1.06		

Reviewer's Comment: *There are no clinically significant differences in visual clarity.*

Burning Profile

The burning profile is determined by assessing the degree of burning at each of 7 postdose time points. Burning is scored on a scale ranging from In this scale, 10% of the scale range is considered clinically relevant. The following graph summarizes the results for burning.



* = Burning significantly more ($p<0.05$) for Voltaren than for Diclofenac 0.1%

Burning Profile

Time (Sec.)		Diclofenac 0.1%	Voltaren	Treatment Difference	Upper 95% Conf. Limit
0	MEAN	5.20	8.40	-3.20	1.31*
	STD	7.75	11.26		
30	MEAN	7.45	14.20	-6.75	-2.23
	STD	8.73	13.45		
60	MEAN	4.80	8.70	-3.90	0.61*
	STD	5.72	11.91		
90	MEAN	2.30	4.35	-2.05	2.46*
	STD	3.87	6.49		
120	MEAN	1.30	2.10	-0.80	3.71*
	STD	2.81	4.06		
150	MEAN	1.05	1.50	-0.45	4.06*
	STD	2.01	2.63		
180	MEAN	0.80	1.15	-0.35	4.16*
	STD	1.70	1.84		

*Equivalence Criteria is satisfied (i.e., treatment difference is less than 10% (5 units) of scale range)

Reviewer's Comment: *Although at the 30- second time point, there is clinically significantly less burning in the Diclofenac group as compared to the Voltaren group, the upper 95% confidence limit at all 7 time points is below the clinically significant limit of 5 units. Therefore, equivalence between the two groups with respect to burning profile can be inferred.*

Safety Outcomes:

Frequency and Incidence of Adverse Events

Coded Adverse Events	Diclofenac 0.1% Ophthalmic Solution N=20		Voltaren 0.1% Ophthalmic Solution N=20	
	N	%	N	%
Ocular				
None	0		0	
Nonocular				
Body as a Whole				
Headache	0		1	5.0
Gastrointestinal				
Gastrointestinal Disorder	1	5.0	0	

Reviewer's Comment: *There were no ocular adverse events reported during the study. There were no serious adverse events reported during the study, nor were any subjects discontinued from the study due to an adverse event.*

Visual Acuity

Maximum Change in Visual Acuity in the **Treated** Eye at Final Visit

Change in Visual Acuity (Snellen Lines)	No Change or Improvement		One Line Decrease		Two Line Decrease		Greater Than a Two Line Decrease	
	N	%	N	%	N	%	N	%
Diclofenac 0.1% and Voltaren 0.1% N=20	18	90	2	10	0		0	

Maximum Change in Visual Acuity in the Untreated Eye at Final Visit

Change in Visual Acuity (Snellen Lines)	No Change or Improvement		One Line Decrease		Two Line Decrease		Greater Than a Two Line Decrease	
	N	%	N	%	N	%	N	%
Diclofenac 0.1% and Voltaren 0.1% N=20	13	65	7	35	0		0	

Reviewer's Comment: *No clinically significant worsening in visual acuity was observed in either group.*

APPEARS THIS WAY
ON ORIGINAL

Reviewer's Conclusions Regarding Comfort and Safety Study # 2

There were no clinically significant differences in comfort between Diclofenac and Voltaren demonstrated in this study.

With respect to safety, there were no clinically significant differences between the two drugs.

Overview of Efficacy

Study # 1 failed to show clinical equivalence between Diclofenac and Voltaren with respect to treatment of anterior chamber inflammation after cataract surgery. Voltaren met the minimum standard for clinical efficacy in this study, whereas, Diclofenac performed 20% below the minimum accepted standard for clinical efficacy.

Overview of Safety

With respect to safety, Diclofenac and Voltaren were equivalent.

The most significant adverse events reported were ocular discomfort, pruritus, hyperemia and tearing.

Labeling Review

Reviewer's Comments: *Labeling will be reviewed at such time as the NDA becomes approvable.*

APPEARS THIS WAY
ON ORIGINAL

Conclusions

Diclofenac is not clinically equivalent to Voltaren and is not clinically efficacious with respect to treatment of anterior chamber inflammation after cataract surgery.

Since Diclofenac and Voltaren are different formulations (see pg. 3 of review), it is possible that this accounts for the difference in their efficacy.

It is the opinion of this reviewer, that a minimum standard for clinical efficacy must be set and strictly adhered to in the drug approval process. It is incumbent upon the drug companies to meet these minimum standards, otherwise, we will begin to approve drugs with less and less efficacy as sponsors request approval for drugs which perform below the minimum standard. Eventually, we will have a situation where the minimum standard drifts downward and the term "efficacy" will become meaningless.

Recommendations

The application, as submitted, is **not recommended** for approval for the indication of treatment of anterior chamber inflammation after cataract surgery.

/S/

Elizabeth N. Ludwig, M.D.

cc: HFD-550
HFD-550/Supervisory CSO/LoBianco
HFD-550/CSO/Holmes
HFD-550/CHEM/Yaciw
HFD-550/MICRO/Stinavage
HFD-550/PHARM/Coulter
HFD-550/BIOPHARM/Bashaw
HFD-550/MO/Ludwig
HFD-550/ActingDivDir/Chambers WAC 6/1/97

Medical Officer's Review of NDA 20-809
Amendment

NDA 20-809	Submission Date:	09/10/97
Review #2	Receive Date:	09/11/97
	Review Date:	11/30/97
	Revised Date:	12/31/97

Drug name:	Diclofenac sodium ophthalmic solution, 0.1%
Generic name:	Diclofenac sodium ophthalmic solution
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 (817) 568-6296
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:	3-S
Related Drugs:	Voltaren® NDA 20-037 Approved 12/31/90

Background Information

The original NDA 20-809, submitted 12/20/96, was not recommended for approval for the treatment of anterior inflammation following cataract surgery. The application failed to demonstrate equivalence to Voltaren using a valid statistical analysis.

On August 29, 1997, a conference call was held between the sponsor and the Ophthalmology Team Leader, Dr. Wiley Chambers. An alternate way of analyzing the data as percentage of cures and percentage of treatment failures was discussed. If the results of this re-analysis were within acceptable limits, approvability of the product might be possible.

The sponsor reanalyzed the data accordingly and submitted it as an amendment to the original NDA.

Amended Statistical Analysis

The statistical objective of this NDA is to demonstrate equivalence between the diclofenac test formulation and Voltaren.

Treatment Failures:

Percent of Treatment Failures*

Intent-to-Treat With Last Observation Carried Forward

	Day 4	Day 8	Day 15
Diclofenac test formulation	1	1	1
Volataren	0	1	1
Placebo	2	12	13

* Patients discontinued with a cell and flare score ≥ baseline score

Failures were defined in the protocol as "patients discontinued with a cell and flare score equal to or greater than baseline score." The data show that 1% of the patients exited from the study in both the Diclofenac test formulation arm as well as in the Voltaren arm. This means that 1 patient from both the Diclofenac test formulation and the Voltaren groups discontinued the treatment prematurely. In contrast, 13 patients discontinued as treatment failures in the placebo arm.

Reviewer's Comment: *With respect to treatment failures, Diclofenac test formulation and Voltaren are equivalent and superior to placebo.*

Percent of Patients Cured*

Intent-to-Treat With Last Observation Carried Forward ( )=95% confidence interval

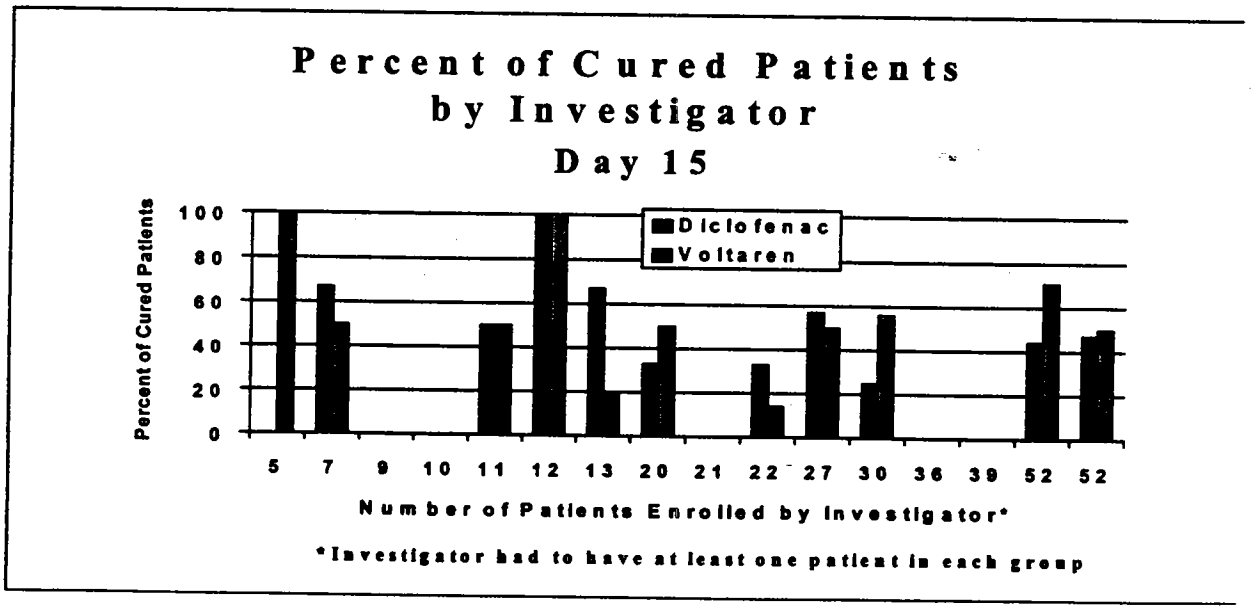
	Day 4	Day 8	Day 15
Diclofenac test formulation	1 (0-3)	6 (2-10)	31 (22-40)
Voltaren	0	11 (5-17)	37 (28-46)
Placebo	0	2 (0-5)	10 (4-16)

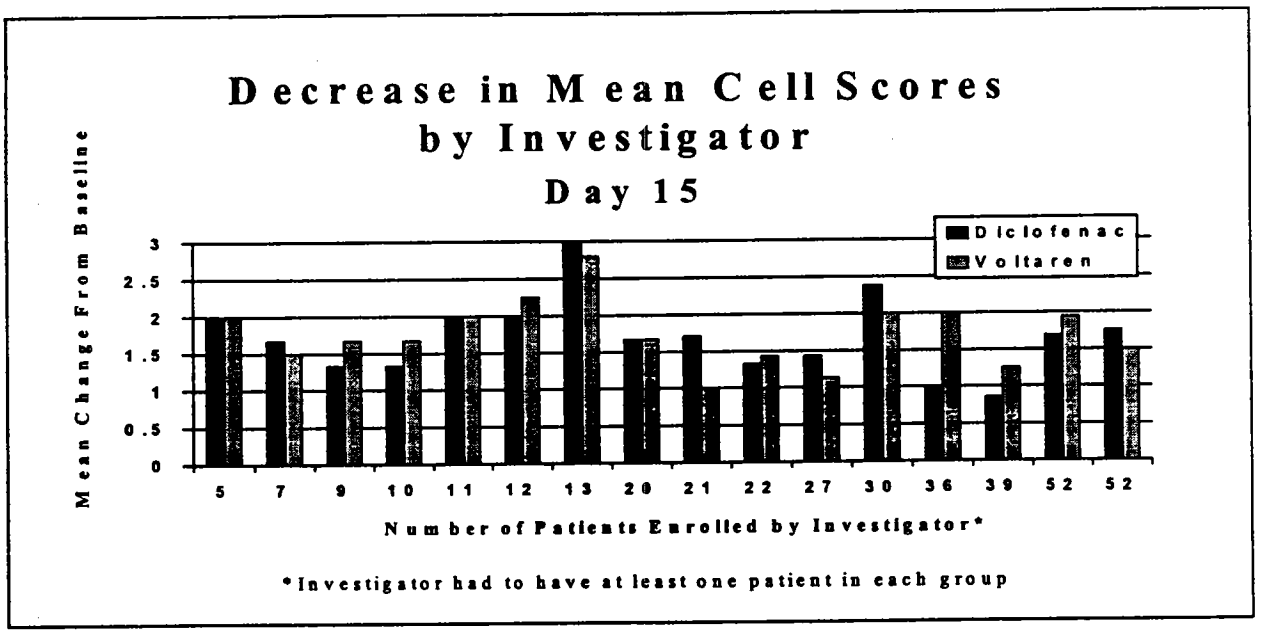
	Day 4	Day 8	Day 15
Voltaren-Diclofenac	-1	5 (-2 to-12)	6 (-6 to 18)

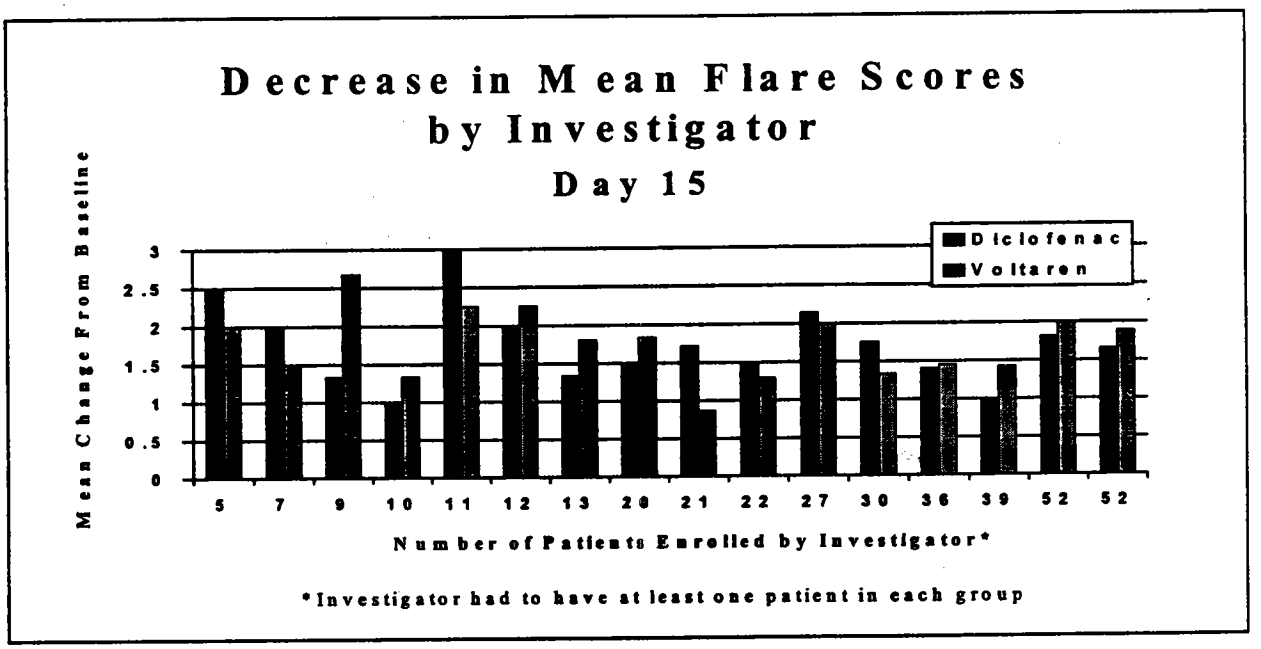
* Patient is cured if cells and flare equal 0 at that day and all subsequent days

Reviewer's Comment: *The confidence interval of the difference between Diclofenac test formulation and Voltaren based on % cures is -6% to 18% which is within the 20 % cut-off rate generally accepted for these types of products demonstrating less than a 70 % cure or success rate. Diclofenac test formulation and Voltaren are considered to be equivalent with respect to efficacy by this analysis.*

Distribution By Investigator:







Reviewer's Comment: *When the data is analyzed and graphed according to investigator, there are fluctuations from one investigator to another as to which product is superior. This is supportive of the equivalence of the two products.*

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

5 pages

Conclusions

Diclofenac Sodium Ophthalmic Solution and Voltaren are clinically equivalent with respect to treatment of anterior chamber inflammation after cataract surgery.

Recommendations

After all Chemistry and Manufacturing deficiencies have been addressed, this application is **recommended** for **approval** for the indication of treatment of anterior chamber inflammation after cataract surgery.

/S/

Elizabeth N. Ludwig, M.D.

cc: Orig NDA 20-809
HFD-550
HFD-550/PM/Gorski
HFD-830/CHEM/Yaciw
HFD-805/MICRO/Stinavage
HFD-550/PHARM/Coulter
HFD-880/BIOPHARM TL/Bashaw
HFD-550/MO/Ludwig
HFD-550/MOTL/Chambers /S/ 12/31/97

Medical Officer's Review of NDA 20-809
Amendment

NDA 20-809	Submission Date:	01/30/98
Review #3	Receive Date:	02/ 3/98
	Review Date:	02/22/98

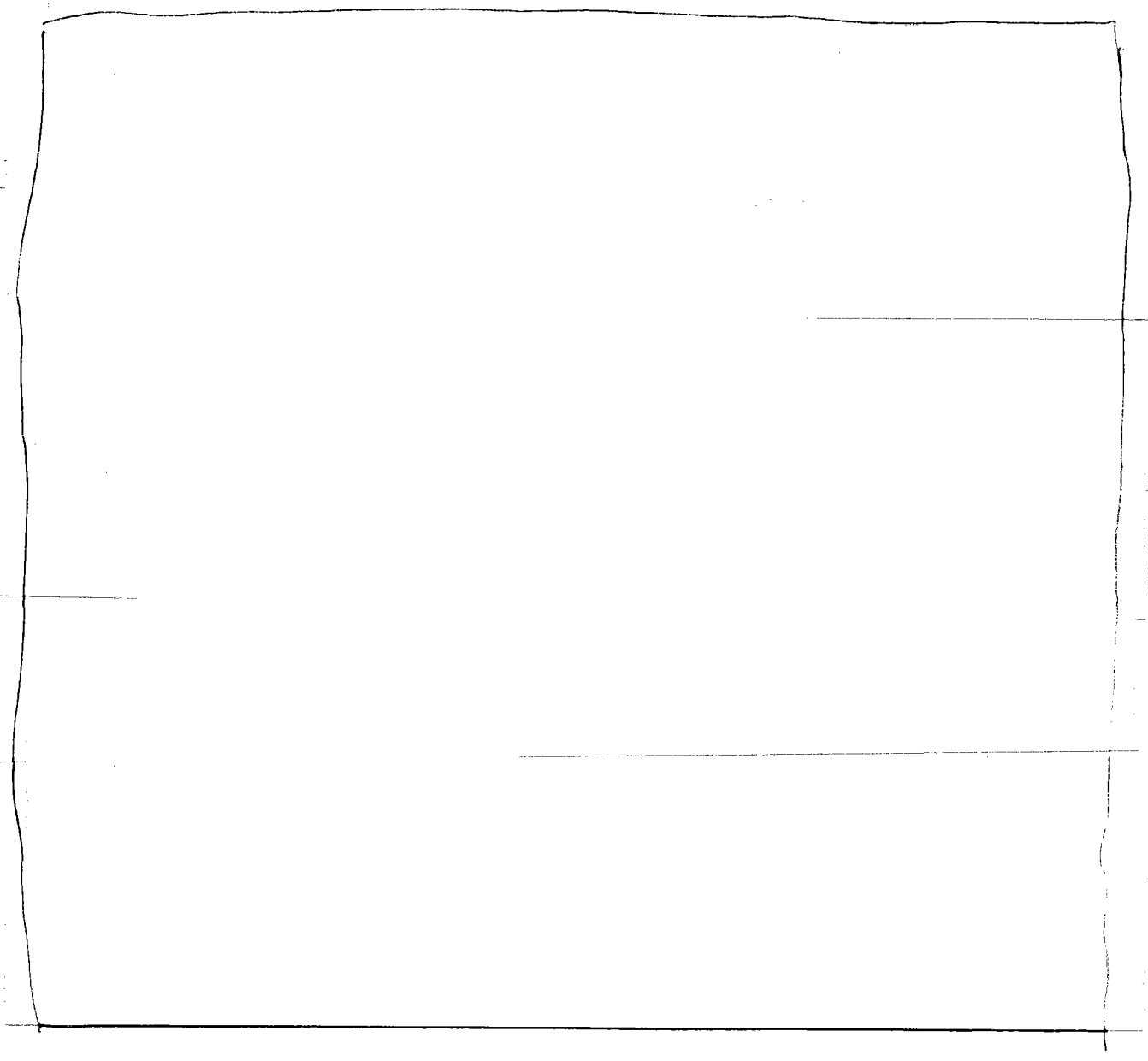
Drug name:	Diclofenac sodium ophthalmic solution, 0.1%
Generic name:	Diclofenac sodium ophthalmic solution
Proposed trade name:	Diclofenac Sodium Ophthalmic Solution 0.1%
Chemical name:	A. Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino Monosodium salt B. Sodium [o-(2,6-dichloroanilino)phenyl]acetate
Sponsor:	Alcon Laboratories, Inc. 6201 South Freeway Fort Worth, TX 76134-2099 (817) 568-6296
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:	3-S
Related Drugs:	Voltaren® NDA 20-037 Approved 12/31/90

Submission: Response to approvable letter dated January 5, 1998.

Issue #1: The submitted labeling is inconsistent and potentially misleading. Please submit revised labeling ...

Response: The revised package insert , bottle and carton labeling are provided in Attachment 1.

Reviewer's Comments: Labeling recommendations are written as follows: recommended deletions are identified by single lines; recommended additions are identified by a double underline. The proposed package insert for Diclofenac Sodium Ophthalmic Solution 0.1% will be essentially the same as the recommended revised package insert for Voltaren of November 1997. The major difference between the two package inserts is the additional approved indication for Voltaren of temporary relief of photophobia after incisional refractive surgery.



THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages

Issue 2: The submitted stability information does not support an expiration date greater than 12 months. Please revise the proposed expiration date to 12 months for all sizes.

Response: Additional stability data have been generated on Diclofenac Sodium Ophthalmic Solution since the NDA amendment of September 10, 1997. To date, eighteen months stability data at the recommended storage conditions have been accumulated on the twelve primary stability lots. These data are presented in Alcon Technical Report Number 003:38420:0198, a copy of which is provided in Attachment 2. The 18 months data in this report demonstrate that the 2.5 mL finished product is physically and chemically stable through 18 months storage at room temperature. In addition, these data indicate that the 5 mL product and 10 mL product* are projected to be physically and chemically stable through 24 months when stored at room temperature. This projection is in part supported by statistical analysis of the available diclofenac concentration assay data on these primary lots. Based on these findings, Alcon proposes an expiration date of 18 months for the 2.5 mL size, and an expiration date of 24 months for the 5 mL size.

* Data on the 10 mL size have been generated. Alcon will only market the 2.5 and 5 mL fill sizes.

Reviewer's Comments: *Acceptable, pending Chemistry/Manufacturing review.*

Issue 3: The submitted information does not adequately address the stability of the drug product when stored in an inverted position. Please submit a plan to provide stability data for this drug product when stored in both the upright and the inverted positions.

Response: In addition to the previously submitted Post Approval Stability Protocol Commitment for samples stored in the upright position, Alcon agrees to evaluate samples stored in the inverted position. Samples from the first three commercial production lots will be evaluated annually for package appearance (sample inspection), visual clarity and color until the desired expiry date of the product is reached. A revised Post Approval Stability Protocol Commitment is provided in Attachment 3.

Reviewer's Comments: *Acceptable, pending Chemistry/Manufacturing review.*

Issue 4: The "Paragraph IV Certification" identifies the wrong patent number. Please provide a revised "Paragraph IV Certification" which addresses United States Patent No. 4,960,799.

Response: A revised "Paragraph IV Certification" which addresses United States Patent No. 4,960,799 is provided in Attachment 4 .

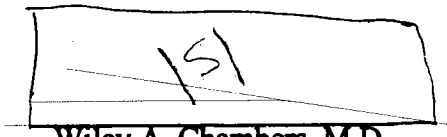
Reviewer's Comments: *Acceptable. Pending legal suits and appeals will need to be resolved prior to final approval.*

Conclusions

Diclofenac Sodium Ophthalmic Solution, 0.1% and Voltaren are clinically equivalent with respect to treatment of anterior chamber inflammation after cataract surgery.

Recommendations

NDA 20-809, Diclofenac Sodium Ophthalmic Solution, 0.1% is recommended for approval for the indication of treatment of anterior chamber inflammation after cataract surgery following resolution of the patent issues.



Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: Orig NDA 20-809
HFD-550
HFD-550/PM/Gorski
HFD-830/CHEM/Yaciw
HFD-805/MICRO/Stinavage
HFD-550/PHARM/Coulter
HFD-880/BIOPHARM TL/Bashaw
HFD-550/MO/Ludwig
HFD-550/MOTL/Chambers

Medical Officer's Review of NDA 20-809
Amendment

NDA 20-809 Review #4	Submission Dates: Receive Dates: Review Date:	4/6/98, 4/21/98 & 4/22/98 4/7/98, 4/22/98 & 4/23/98 4/27/98

Drug name:	Diclofenac sodium ophthalmic solution, 0.1%
Generic name:	Diclofenac sodium ophthalmic solution
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 (817) 568-6296
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:	3-S
Related Drugs:	Voltaren® NDA 20-037 Approved 12/31/90

Submission: Response to "tentative approval letter dated March 23, 1998.

Reviewer's Comments: *Acceptable.*

2. Safety Update

Study Information for Studies:

C-95-29	Discontinued	27 patients	Results pending
C-95-30	Discontinued	40 patients	Results pending
C-96-01	Discontinued	8 patients	Results pending
C-95-55	Discontinued	53 patients	Results pending
C-96-70	Ongoing	380 patients	Results pending

The discontinued studies are listed as discontinued for "business reasons and not safety reasons." Events are listed in an unblinded table.

Event	C-95-29	C-95-30	C-96-01	C-95-55	C-96-70
Abnormal Vision			1		
Allergic Reaction					3
Allergy	1				1
Arthritis				1	
Bradycardia				1	
Cold syndrome	1	1			
Conjuntival follicles					2
Corneal lesion					1
Corneal ulcer					1
Corneal staining					1
Corneal infiltrate					1
Cyclitic membrane					1
Descemetitis				1	
Diarrhea				1	
Discomfort		5	1		8
Dizziness				1	
Dry Eye	3				
Edema Eye/Conjunctiva			1		2
Endophthalmitis				1	2
Erythema		1			
Fibrin increased					4

Glaucoma					1
Headache	1	1			
Hyperemia					19
Hypopyon				1	
Hypotony				1	1
Increased IOP					1
Keratitis	5		2		9
Keratopathy	2				
Lid margin crusting					1
Lid edema					1
Macular edema					1
Pain					5
Photophobia					1
Pruritis					2
Rash (macular/papular)					1
Retinal detachment					1
Stromal edema					1
Subconjunctival hemorrhage					2
Syncope				1	
Taste perversion	1				
Tearing			1		2
Urinary Retention					1
Vascular disorder					1
Vision blurred			1		
Vomiting	1			1	

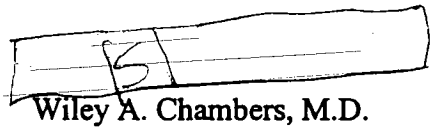
Reviewer's Comments: *The number of cases of endopthalmitis is higher than would be expected, however, the cases are evenly split between groups and therefore it is less likely to be related to the change in formulation. The events are otherwise consistent with previous reports for this drug in this dosage form.*

3. No changes have been made to the labeling, chemistry, manufacturing and controls since the date of the tentative approval letter. An amendment for an alternate manufacturing site was submitted on March 26, 1998, and withdrawn on April 3, 1998.

Reviewer's Comments: *Acceptable.*

Recommendations

NDA 20-809, Diclofenac Sodium Ophthalmic Solution, 0.1% is recommended for approval for the indication of treatment of anterior chamber inflammation after cataract surgery.



Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: Orig NDA 20-809
HFD-550
HFD-550/PM/Gorski
HFD-830/CHEM/Yaciw
HFD-805/MICRO/Stinavage
HFD-550/PHARM/Coulter
HFD-880/BIOPHARM TL/Bashaw
HFD-550/MO/Ludwig
HFD-550/MOTL/Chambers