

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020809**

**PHARMACOLOGY REVIEW(S)**

HFD-550

Holmes

MAR 7 1997

THE DIVISION OF ANTI-INFLAMMATORY, ANALGESIC,  
AND OPHTHALMIC DRUG PRODUCTS

PHARMACOLOGY/TOXICOLOGY REVIEW  
REVIEW N<sup>o</sup> 1

NDA 20-809

DRUG: Diclofenac Sodium Ophthalmic Solution 0.1%

SPONSOR: Alcon Laboratories, Inc.  
Fort Worth, Texas 76134

SUBMISSION DATE: December 20, 1996

REVIEWER: A. W. Coulter, Ph.D.

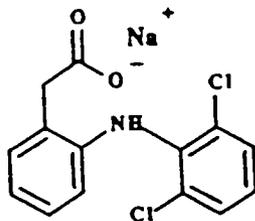
DATE ASSIGNED: January 2, 1997

REVIEW COMPLETED: February 28, 1997

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FORMULATION:

<u>Ingredients</u>	<u>Percent w/v</u>	<u>mg/mL</u>
Diclofenac Sodium		
Polyquaternium-1		
Tocophersolan		
Mannitol		
Boric Acid		
Hcl/NaOH		To adjust pH
Purified Water		



2-[(2,6-dichlorophenyl)amino]benzeneacetic acid, monosodium salt  
USAN Name: Diclofenac sodium  
CAS Registry N<sup>o</sup> 15307-79-6

C<sub>14</sub>H<sub>10</sub>Cl<sub>2</sub>NO<sub>2</sub>Na

Mol. Wt: 318.13

**DRUG CATEGORY:** NSAID

**PROPOSED MARKETING INDICATION:** Postoperative inflammation after cataract surgery.

**DOSAGE/ADMINISTRATION:**

Cataract surgery: One drop qid for 2 weeks.  
Incisional Refractive Surgery: One drop within 1 hour of surgery; one drop within 15 minutes after surgery; one drop qid up to 3 days.

**PRECLINICAL STUDIES:** This NDA was submitted under 505(b)(2).

**PHARMACOLOGY**

- a) Diclofenac Sodium (AL-3157A): Summary of Current Preclinical pharmacology. Report N<sup>o</sup> 011:39900:0595
- b) Preclinical Evaluation of a Proposed Clinical Formulation of Diclofenac Containing Vitamin E TPGS. Report N<sup>o</sup> 001:39900:0296.

**TOXICOLOGY**

Ocular Studies Conducted with Diclofenac Ophthalmic.

- a) On-Month Interim Report From the Three-Month Topical Ocular Irritation and Systemic Toxicity Evaluation of Diclofenac Ophthalmic Solution in Rabbits. Report N<sup>o</sup> 030:38520:0196, Alcon Laboratories, Inc.
- b) Three-Month Topical Ocular Irritation and Systemic Toxicity Evaluation of Diclofenac Ophthalmic Solution in Rabbits. Report N<sup>o</sup> 070:38520:0496, Alcon Laboratories, Inc.
- c) One-Month Interim Report From the Three-Month Topical Ocular Irritation and Systemic Toxicity Evaluation of Diclofenac Ophthalmic Solution in Rabbits. Report N<sup>o</sup> 092:38520:0695, Alcon Laboratories, Inc
- d) Three-Month Topical Ocular Irritation and Systemic Toxicity Evaluation of Diclofenac Ophthalmic Solution in Rabbits: Report N<sup>o</sup> 104:38520:0895, Alcon Laboratories, Inc

Ocular Studies Conducted with the Preservative POLYQUAD®.

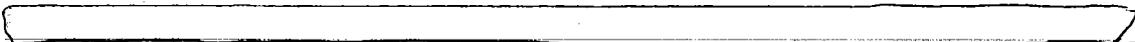
- a) One-Year Chronic Topical Ocular Irritation Evaluation of POLYQUAD in Rabbits. Report N<sup>o</sup> 005:3320:0385

**Pharmacokinetics/Drug Metabolism**

- a) Diclofenac Concentrations in Aqueous Humor and Plasma Following a Single Bilateral Dose of 0.1% Diclofenac Ophthalmic Solution in Male New Zealand Rabbits. Report N<sup>o</sup> 043:38570:0896

- b) Diclofenac Plasma Concentrations From Toxicology Study N-95-220: Three Month Topical Ocular Irritation and Systemic Toxicity Evaluation of Diclofenac Ophthalmic Solution in Rabbits.  
Report N° 035:38570:0796
- c) Distribution of Radioactivity in Ocular Tissues Following a Single Topical Ocular Dose of 0.1% Diclofenac Ophthalmic Solution Containing 5% [<sup>14</sup>C-Polyethylene glycol 1000]-Tocophersolan to Male New Zealand White Rabbits.  
Report N° 049:38570:1096

**RELATED DRUGS/INDs/NDAs:**



- NDA 19-201 Voltaren® Tablets (diclofenac sodium), Ciba Geneva Pharmaceuticals
- NDA 20-037 Voltaren Ophthalmic 0.1% Sterile Solution (diclofenac sodium), Ciba Vision Ophthalmics
- NDA 20-142 Cataflam (diclofenac potassium), Ciba Geneva
- NDA 20-254 Voltaren-XR (diclofenac sodium), Geigy

**Abbreviations Used In This Review**

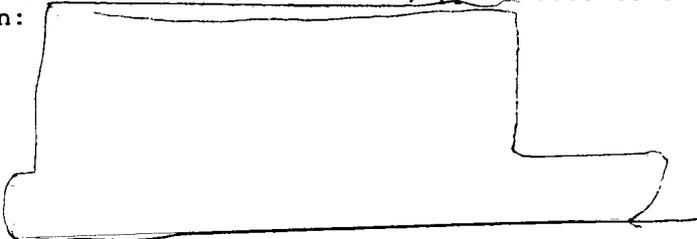
D = day(s)	DR = dose related	G = group(s)	* = p<0.05
OD = right eye	OS = left eye	** = p<0.01	

**PHARMACOLOGY:**

**DICLOFENAC SODIUM (AL-3157A): SUMMARY OF CURRENT PRECLINICAL PHARMACOLOGY:**

Report N°: 011:39900:0595; Vol. 1.6, pp. 5-0005 to 5-0010

Formulation:



"The proposed formulation (FID# 88281, Experiment 1) was identical in composition to the final clinical formulation (FID# 89565, Experiment 2), differing only in the batch quantity prepared."

The above formulation was evaluated for its ability to inhibit cyclooxygenase activity *in vitro* in sheep vesicular glands and *ex vivo* prostaglandin E<sub>2</sub> synthesis [redacted] in the iris ciliary body. The ability to prevent blood-aqueous breakdown in a rabbit model mimicking surgery-induced ocular trauma was also evaluated (N° of rabbits not indicated).

**RESULTS**

- cyclooxygenase activity *in vitro*: diclofenac sodium [redacted] indomethacin [redacted]
- *ex vivo* PGE<sub>2</sub> inhibition: 85%

• trauma-induced breakdown of blood-aqueous barrier:

	Exp. 1	Exp. 2	Average
Alcon's proprietary formulation:	52%	66%	59%
Voltaren	53%	63%	58%

There were no large changes between VOLTAREN (diclofenac sodium 0.1%) and Alcon's proprietary formulation of diclofenac

The formulation used in the protein influx into the anterior chamber following paracentesis differed from that indicated in the above study description. In addition, the study did not indicate the number of rabbits used in determining protein influx, and standard deviations were large.

PRECLINICAL EVALUATION OF A PROPOSED CLINICAL FORMULATION OF DICLOFENAC CONTAINING VITAMIN E TPGS:

Report N<sup>o</sup> 004:39900:0296; Vol. 1.6, pp. 5-0011 to 5-0013

This study evaluated the ability of Alcon's proposed clinical formulation to inhibit protein influx into the anterior chamber of the rabbit eye following paracentesis. Alcon's proposed clinical formulation (pH 6.7) used in this study contained 0.1% diclofenac.

A single 50 µL dose of the formulation was applied to each eye of NZW rabbits (4/group). The data were compared to vehicle and Voltaren 0.1% (Geigy).

The results indicated Alcon's formulation to be equivalent to Voltaren 0.1% in reducing protein influx. Significance was observed with both the Alcon formulation and Voltaren, when compared to the vehicle or PBS.

**TOXICOLOGY:**

THREE-MONTH TOPICAL OCULAR IRRITATION AND SYSTEMIC TOXICITY EVALUATION OF DICLOFENAC OPHTHALMIC SOLUTION IN RABBITS:

Report N<sup>o</sup>: 070:38520:0496; Vol. 1.6, pp. 5-0047 to 5-0353-70

Protocol N<sup>o</sup>: N-95-220

Route: Ocular, topical 4x/day

Diet: Approximately one cup/day

Groups: G1 (untreated)

G2 [vehicle 1 + benzyldimethyldodecyl ammonium bromide (BAB)]

G3 (0.1% diclofenac + BAB),

G4 (vehicle 2 + POLYQUAD)

G5 0.1% diclofenac + POLYQUAD),

G6 (0.1% diclofenac + sorbic acid)

## Formulations:

From Volume 1.6, p. 5-0069

Ingredients	CONCENTRATION (W/V %)				
	Group 2 Vehicle 1	Group 3 0.1% Diclofenac	Group 4 Vehicle 2	Group 5 0.1% Diclofenac	Group 6 0.1% Diclofenac
Diclofenac Na	0	0.1	0	0.1	0.1
	3.0	3.0	5.0	5.0	-
Mannitol	1.0	1.0	3.5	3.18	-
NaCl	0.2	0.2	-	-	-
	-	-	-	-	0.1
	-	-	-	-	4.5
	-	-	-	-	0.2
	-	-	-	-	0.85
Boric Acid	1.2	1.2	1.2	1.2	1.4
	0.016	0.016	-	-	-
	-	-	0.005	0.005	-
	0.1	0.1	0.1	0.1	-
HCl/NaOH	qs pH to 6.0±0.4	qs pH to 6.0±0.2	qs pH to 6.7±0.2	qs pH to 6.7±0.2	qs pH to 7.2±0.4
Purified Water	qs to 100	qs to 100	qs to 100	qs to 100	qs to 100

<sup>1</sup> Benzyltrimethylammonium bromide<sup>2</sup> Polyquaternium-1<sup>3</sup> Hydroxypropyl methylcellulose

Strain: NZW, 2.4 Kg to 2.9 Kg body weight.

Number: 10/sex/group

Study Site: Alcon Laboratories, Inc., Fort Worth, TX

Date: December 13, 1995 to September 3, 1996

GLP/QAU: Both present and signed.

The purpose of this study was to determine the ocular irritation potential and systemic toxicity of 0.1% Diclofenac Ophthalmic Solution following qid ocular administration to rabbits for three months. The study contained two control vehicles, one untreated control, and three formulations of 0.1% diclofenac.

Four rabbits per group were assigned to the one-month interim evaluation (Report N<sup>o</sup> 030:38520:0196). The remaining 5/group were treated for 91-92 days. All animals were treated with two drops (70 µL) applied to the right eye at 8:00 a.m., 10:30 a.m., 1:00 p.m., and 3:30 p.m. The left eye served as the untreated control. All animals were examined twice/week prior to dosing. Body weight was determined prior to Day 0 and on D7, 14, 21, 28, 35, 49, 63, 77, 91 and prior to necropsy. Biomicroscopic examinations were done prior to D(0) and on D7, 21, 35, 49, 63, 77, and 91. Indirect ophthalmoscopic examinations were performed on D(0), D35, and D91. Pachymetry (corneal thickness) was measured D(-1), D34 and D90 for both eyes. Clinical

evaluations included hematology (14 parameters) and serum chemistry (23 parameters) were determined D90-91. Blood was collected on D1, D30, D45, and D87 for determination of diclofenac concentrations. Necropsy was conducted on D92 and 93. Organ weights were determined for the liver, gonads, adrenals, heart, kidneys, brain, and spleen. The eyes, adnexa, and nasal lacrimal tissue from all animals, and all collected tissues from the untreated G1 and G5 were submitted for histopathologic examination.

#### RESULTS AND DISCUSSION

##### Observed Effects/Mortality/Body Weight:

- 1♂G3 (N<sup>o</sup> 93698) ocular discharge OD, D34 and 90-
- 1♂G3 (N<sup>o</sup> 93703) small diarrhea D6 - tail skin red/irritated D90 and D92-
- 1♂G6 (N<sup>o</sup> 93669) stool mucus/loose stool D14 - diarrhea D58-
- no premature deaths-
- no significant (\*) difference between groups - ♂ body wts of G2-6 were below G1 by 7.3%-10% - ♀ body wts were below G1 0.6%-8.9%-

##### Ocular Evaluation:

- pachymetry indicated no significant difference between groups-
- minimal hyperemia and conjunctival congestion in all groups-
- no conjunctival swelling/discharge noted throughout the one-month period-
- one minimal aqueous flare G2 OD D35-
- no iritis or corneal cloudiness reported in any group-
- no fluorescein staining during the one-month period-
- no lenticular changes or neovascularization in any group-
- optic nerve head and major retinal and choroidal vessels found to be within normal limits at evaluation-

##### Hematology: results were compared to untreated group G1

- MCHC ↓ ♀G2 and ♀G3 (p = 0.0156, 3.4%, 4%) within historic control range-
- Hct ↓ ♂G4 (vehicle 2), p = 0.00005 (9.3%)-
- Hb ↓ ♂G4 (p = 0.0001, 9.4%); ↓ ♂ G5 and G6 (p = 0.0001, 7.9%, and 7.5%, respectively - values were within historic control limits-
- eosinophils ↓ significantly ♀G5 but within historic controls-

##### Serum Chemistry: results were compared to untreated G1

- albumin/globulin ratio ↓ ♂G5 (p = 0.0418, 11.8%)-
- globulin ↓ G4 (p = 0.0173, 15.6%)-
- sodium ↓ G3, G4, G5 (p = 0.0118, 2.6%, 2.9%, 2.3%, respectively)-

##### Gross Pathology: (conducted by Experimental Pathology Labs., Herndon, VA)

- no gross lesions of eyes, adnexa, or nasal-lacrimal tissues-
- G5 ♀ (N<sup>o</sup> 93773) 75 cc clear peritoneal fluid-
- ♀ (N<sup>o</sup> 93719) 0.5 cm<sup>3</sup> parovarian cyst, left side-
- ♀ (N<sup>o</sup> 93769) bilateral markedly pitted kidney-
- G6 ♀ (N<sup>o</sup> 93776) 75 cc clear peritoneal fluid-

##### Organ Weights:

- kidney, absolute ↓ ♂[G3 (p = 0.0114, 16.7%), G4 (p = 0.0114, 13.5%)-

##### Gross Observations:

- eyes, adnexa, and nasal-lacrimal tissues had no gross lesions-

Histopathology:

Ocular Incidence Summary Table  
 (n = 10/sex/group)  
 (Vol. 1.6, Pages 5-0305 to 5-0314)

	G1 L	G1 R	G2 L	G2 R	G3 L	G3 R	G4 L	G4 R	G5 L	G5 R	G6 L	G6 R
Cornea: limbus MN cell infilt.	3	2	2		2	1	1	1	3	2	2	4
Eyelid: MN cell infiltrate epidermis, erosion epidermis, hyperplasia	4	3	3		3	1	3 1 1	1	3	2	3	5
Harderian Gland: MN cell infilt. atrophy	3 1	1		1	1	2	1 1	2			1 1	1
Lacrimal Gland: MN cell infilt. atrophy	1		2	2	1	1	1	3		3	2	3 1
Nasal Turbinate: hemorrhage, acute	2	1					1				1	2
Nasolacrimal Duct: hemorrhage, acute		6	2	3	1	5	3	3	2	2		2
Nictitating Membrane: MN cell infilt.	1	3	2	1	2			1	2	1	2	1
Retina: folds			2			1						

The bolded columns (G2R, G3R, G4R, G5R, G6R) indicate the treated right eyes.

- no significant lesions observed in large or small intestine-
- erosion was reported in the stomach fundus of 1/5 ♀G5 (slight/mild)-
- liver: chronic inflammation 1♀G5 (minimal), 1♂1♀G6 (minimal)-
- kidney: interstitium, fibrosis 1♀G5 (moderate), 1♀G6 (slight/mild)-
- seminiferous tubules: unilateral degeneration 1♂G6 (minimal)-
- brain: nonsuppurative inflammation in cerebral cortex 1♀G5 (minimal)-  
mononuclear cell infiltrate in meninges 1♀G5 (minimal)-
- other lesions were spontaneous and did not appear to be treatment related-

**APPEARS THIS WAY  
ON ORIGINAL**

Plasma Diclofenac:

Mean Diclofenac Plasma Concentrations Without  
 Regard to Sex of Animals  
 (Vol.1.6, Page 5-0353-4)

DAY	PLASMA CONCENTRATION (ng/mL) GROUP 3 0.1% DICLOFENAC/BAB			
	PEAK		TROUGH	
	MEAN	STD	MEAN	STD
1	12.7	3.7	5.38	1.09
30	9.21	2.48	3.65	1.36
45	11.3	3.9	3.49	1.36
87	9.94	2.66	3.01	1.06
DAY	PLASMA CONCENTRATION (ng/mL) GROUP 5 0.1% DICLOFENAC/POLYQUAD			
	PEAK		TROUGH	
	MEAN	STD	MEAN	STD
1	10.6	4.0	5.24	2.20
30	11.3	4.6	4.75	1.58
45	14.9	4.3	5.38	1.70
87	11.4	2.8	4.72	1.64
DAY	PLASMA CONCENTRATION (ng/mL) GROUP 6 0.1% DICLOFENAC/SORBIC ACID			
	PEAK		TROUGH	
	MEAN	STD	MEAN	STD
1	8.55	2.19	4.34	1.04
30	8.24	2.05	3.27	0.96
45	7.31	2.46	3.04	0.89
87	6.92	1.39	2.24	0.54

There were no sex related differences in the mean peak concentrations of any group. Mean values were similar in G3 and G4 and somewhat lower in G6.

## SUMMARY

Isolated instances of clinical signs and ocular changes were observed, but none appeared to be related to the treatment. Serum chemistry and hematology changes that were reported were within the reference range for this laboratory; however, it is clear that changes were produced by the two vehicles and the three 0.1% diclofenac solutions.

The chronic renal inflammation and interstitial fibrosis and nonsuppurative brain inflammation in one G5 female were said to be consistent with infestation by *Encephalitozoon cuniculi*, a common microsporidial parasite

of rabbits. Systemic drug exposure was seen with the three 0.1% diclofenac formulations, with no differences occurring between males and females, and no statistical differences between the peak plasma concentrations from Day 1 to Day 87.

The number of plasma samples analyzed was 240 (pp. 5-0353-39 to 5-0353-45), one more than the number of samples received (p. 5-0353-34). In general, this submission was not well organized and difficult to review.

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THREE-MONTH TOPICAL OCULAR IRRITATION AND SYSTEMIC TOXICITY EVALUATION OF DICLOFENAC OPHTHALMIC SOLUTION IN RABBITS:

Report N<sup>o</sup>: 104:38520:0895; Vol. 1.6, pp. 5-0354 to 5-0680 in Vol. 1.7  
Protocol N<sup>o</sup> N-95-51

Route: Ocular, topical qid

Diet: Approximately 1 cup/day

Strain: NZW, 2.5 to 2.9 Kg body weight

Number: 9/sex/group (5/sex/group were treated for 91 days)

Groups: Group 1 (untreated)

Group 2 (vehicle)

Group 3 (0.1% diclofenac)

Group 4 (0.2% diclofenac)

Group 5 (Voltaren)

Study Site: Alcon Laboratories, Inc., Fort Worth, TX  
Date: May 10, 1995 to September 3, 1996  
GLP/QAU Statements: Both present and signed.

The study was done to determine the ocular irritation following a three-month administration of Diclofenac Ophthalmic Solution 0.1% and 0.2% when administered four times/day to rabbit eyes.

#### METHODS

Animals in G2, G3, and G4 received 2 drop applied to the right eye only on D1-D14. On D15-D91 they received 1 drop ( $\approx 60 \mu\text{L}$ ). The Voltaren group (G5) received 2 drops ( $\approx 60 \mu\text{L}$ ) in the right eye throughout the study. Left eyes served as a contralateral untreated control. Animal were observed twice/day. Body weights were recorded pretesting and on D7, D14, D21, D35, D49, D59, D77, D91, and prior to necropsy on D92. Bimicroscopic examinations were done on both eyes on D(0) and on the weighing days. Indirect ophthalmoscopic examinations were done D(0), D35, and D91. Corneal thickness was recorded on D(-2), D34, and D91. Clinical chemistry (23 parameters) and hematology (9 parameters) were evaluated D87. Blood was collected for plasma diclofenac concentrations in G3 and G4, but due to a change in the development, plasma concentrations were not determined.

Necropsy was done on D92. Organ weights were recorded for the liver, gonads, adrenals, heart, kidney, brain, and spleen. Histopathology was evaluated in all groups on the anterior chamber, choroid, ciliary body, cornea, eyelid, Harderian gland, iris, lacrimal gland, lens, nictitating membrane, optic nerve, retina, and sclera. Histopathology on other tissues was evaluated only in the control (G1), 0.1% diclofenac (G3), and 0.2% diclofenac (G4). Four/sex/group were assigned to a one month interim group for sacrifice after one month. This interim G4 contained 5 $\sigma$  instead of 4 $\sigma$  and 4 $\phi$ , as one of the  $\sigma$  was incorrectly sexed and placed in the study as a  $\phi$ .

#### RESULTS AND DISCUSSION

##### Observed Effects:

- Group 1: all were normal throughout study-
- Group 2: several small scabbed areas on head of  $\sigma$  N $^{\circ}$  85807
- Group 3: all were normal throughout study-
- Group 4: small amount of soft stool D9 and swollen digit  $\sigma$  N $^{\circ}$  85786-  
hair chewing and scabbed chest  $\phi$  N $^{\circ}$  85758
- Group 5: hair loss under chin - dry red area inside ear  $\sigma$  N $^{\circ}$  85798-  
raw/scabbed/hairless area below nasal corner of eye - hair loss  
encircling OD-

Body Weight: no significant differences between treated groups when compared to untreated control - G4  $\sigma$  (0.2% Diclofenac) weight gain was 6% less when compared to G3 (0.1% Diclofenac)-

Ocular Examination: minimal conjunctival congestion in all groups - conjunctival swelling occurred in OD of 1 $\sigma$  D21, G4 - no conjunctival discharge, changes in light reflex, aqueous flares, iritis, corneal cloudiness, fluorescein staining, lens changes, or neovascularization reported in any group-

Indirect Ophthalmoscopy: optic nerve head and major retinal and choroidal vessels were said to be within normal limits in both treated and control eyes on treatment initiation, D35, and D91-

Pachymetry: statistically significant ↓ from baseline in G3 ♀ D91 when compared to G1 - no significance in G4 (no dose response)-

Hematology: DR non-significant ↓ ♂♀ diclofenac Hct/Hb/RBC from G1 and G2-  
DR non-significant ↓ ♂ lymphocytes (diclofenac and voltaren)-

Serum Chemistry: (DR, non-significant changes from untreated control)  
↓ ♂♀ alb/glob ratio, globulin, and ALT (diclofenac)-  
↓ ♂ cholesterol, urea nitrogen, and glucose (diclofenac)-  
↓ ♂ CPK (diclofenac)-  
↓ ♀ GGT and globulin (diclofenac)-

Significant Changes in Serum Chemistry

↑ ♀ glucose (diclofenac G3 and G4)-  
↑ ♀ Ca, total protein, and globulin.(vehicle)-  
↑ ♀ phosphorus (G4 and G5), DR for diclofenac-  
↑ ♀ sodium (vehicle and voltaren)-

Organ Weights: ♂ gonads - absolute wt G3 ↓ (\*, 31.6%)-  
♀ heart - absolute wt G3 ↓ (\*, 16.2%)-

Gross Pathology: one or two animals in each group had multiple pinpoint bilateral cysts adjacent to one or both ovaries and one animal in G4 had mildly pitted kidneys-

Histopathology:

Three-Month Sacrifice (n = 10, 5/sex/group)

	G1 OS	G1 OD	G2 OS	G2 OD	G3 OS	G3 OD	G4 OS	G4 OD	G5 OS	G5 OD
Eyelid: mononuclear cell infiltrate, focal mononuclear cell infiltrate, multifocal Polymorphonuclear cell infiltrate, focal	1		1	1	1 2	1 1	2 1	1	2	2
Nictitat. membr: mononuclear cell inflt., focal lymphoid follicle, focal	#	1				2		1 1	1	1
Retina: degeneration, focal rosette(s)		1 1	3	3		1		1	2	1 1
Sclera: infiltrate, mononuclear cell, focal	4	3	3	3	1		3	5	3	5

Bolded columns indicate the treated right eyes.

# n = 9

Other incidental changes occurred in the eyes, adnexa, and nasal lacrimal tissue but also did not appear to be treatment related.

- intestinal tract: no lesions reported-
- stomach: mononuclear cell infiltrates in G1, G3, and G4 (not dose related)-
- kidney multifocal cast(s) 1 ♂G3  
glomerulosclerosis, multifocal 1 ♂G4  
infiltrate, mononuclear cell, multifocal 1G1♂, 1G3♂♀, 1G4♂, 2♀G4-  
mineralization, multifocal ♂ (3G1, 2G3, 3G4), ♀ (1G1, 2G3)  
renal tubule, regen., multifocal ♂ (2G1, 1G3, 1G4), ♀ (1G3, 1G4)-  
infarct(s), multifocal ♀ 1G4-
- other lesions were incidental and not treatment related-

SUMMARY

No mortality or moribundity occurred during the study. The observed effects that occurred in one or two animals of G2, G4, and G5 were not adverse. A 6% decrease in weight gain occurred in the 0.2% Diclofenac group.

The indirect ophthalmoscopy and ocular examinations did not result in any significant changes; however, there was a significant (p=0.0073) increase in corneal thickness of G3 from baseline to D91, when compared to the untreated group (G1 Δ = 19 mm, G3 Δ = 29 mm, 53%). Significant increases occurred in serum glucose in G3 and G4, and phosphorus was significantly increased in G4 and G5. No gross lesions were reported for the eyes, adnexa, or nasal tissues. The histopathologic examination of other tissues indicated no treatment related changes.

ONE-YEAR CHRONIC TOPICAL OCULAR IRRITATION EVALUATION OF POLYQUAD IN RABBITS:

Report N<sup>o</sup>: 005:3320:0385; Vol. 1.7, pp. 5-0681 to 5-1233 in Vol. 1.8

Protocol N<sup>o</sup>: N-82-73

Route: Topical, ocular

Diet: [redacted] and 5325 *ad libitum*

Strain: NZW, 1.7 Kg to 3.0 Kg body weight

Number: 12/sex/group

Route: Topical, ocular - 2 drops in OD 3x/day

- Groups: G1 Untreated control  
 G2 Polyquad 0.001%  
 G3 Polyquad 0.01%  
 G4 Polyquad 0.05%  
 G5 Thimerosal 0.001%  
 G6 Benzalkonium Chloride (BAC) 0.01%

Formulation:

	Group 1 Polyquad 0.001%	Group 2 Polyquad 0.01%	Group 3 Polyquad 0.05%	Group 4 Thimerosal 0.001%	Group 5 BAC 0.01%
Polyquad	0.001	0.01	0.05	-	-
Sodium Chloride	0.7	0.7	0.7	0.7	0.9
Boric Acid	0.35	0.35	0.35	0.35	-
<span style="border: 1px solid black; padding: 2px;">[redacted]</span>	qs pH 7.4	qs pH 7.4	qs pH 7.4	qs pH 7.4	-
	-	-	-	0.001	-
	-	-	-	0.1	-
	-	-	-	-	0.01
Purified Water	qs	qs	qs	qs	qs

Study Site: Alcon Laboratories, Inc., Fort Worth, Texas.

Date: March 30, 1983 to April 6 1984. The compliance statement was signed and dated September 3, 1996.

GLP/QAD: Both present and signed.

The purpose of this study was to determine the chronic ocular irritation and systemic toxicity potential of the preservative, Polyquad. At six months an interim sacrifice of 5/sex/group was conducted; the remaining animals were further treated and sacrificed at 12 months. Treatment consisted of 2 drops in the right eye (60 µL) administered at 8:00 am, 11:30 am, and 3:00 pm every day except D260. "Right eyes of the control animals were physically manipulated as those eyes which received a test or control article."

The study included daily evaluation for general condition of the animals. Body weight was determined prior to starting treatment and monthly. Slit-lamp biomicroscopic examinations were done pre-treatment and at approximately one hour after the last daily treatment on D1, 7, 14, 30, and monthly thereafter. Indirect ophthalmoscopic examinations were carried out four days before the first treatment and at approximately 3-month intervals. Necropsy and histopathology were evaluated on 36 tissues/organs. Necropsy was done on all moribund animals and animals found dead. Histopathology included evaluation of the eyes, eyelids, nictitating membranes, lacrimal/Harderian glands, brain, nasal cavity, nasolacrimal duct, liver, kidneys, and any gross lesions from animals in any group. In addition, the heart, spleen, pancreas, stomach, pituitary, adrenals, gonads, and small intestine were evaluated in Groups 1, 4, 5, and 6. Scanning electron microscopy was evaluated on corneas (OD and OS) of two randomly selected animals from each group at both the interim and final sacrifice. The study did not look at hematology, serum chemistry, or urinalysis.

#### RESULTS AND DISCUSSION

- observed effects: nasal discharge, nonspecific hair loss, loose or no stools, diarrhea, ocular discharge, and torticollis were observed in all groups and appeared to be sporadic and random-
- mortality: (from Vol. 1.7, Table 5, p. 5-0695)
 

	G1	G2	G3	G4	G5	G6
moribund sacr.:	3/24	1/14	1/24	1/24	0/24	1/24
mortalities:	5/24	3/24	2/24	6/24	2/24	8/24
Total:	8	4	3	7	2	9

The possible causes of moribundity and mortality of these animals were said to be due to mucoid enteropathy, multifocal suppurative bronchopneumonia, and bacterial infection (*Pasteurella?*). Mortality did not appear to be treatment related. The mortality rate, however, was excessive for this type of study. It appears these animals were not examined and certified to be disease free for the study.

	Total Incidence - male(female)					
	G1	G2	G3	G4	G5	G6
Mucoid enteropathy	-	-	-	-	-	-
M.s. bronchopneumonia	-	1(1)	-	(2)	-	(1)
Bacterial infection	-	-	-	-	-	-

Ten rabbits died or were sacrificed moribund between six and 12 months, with 5/10 of these in the untreated control group. "The five deaths or moribund sacrifices from the treated animals were not considered to be related to the treatment used in this study but probably from pneumonia or a trichobezoar obstruction of the stomach."

- body weight: ↓ ♀G5 D119 (\*,13%) and D148 (\*,14.6%) from G1-
- ocular evaluation:
  - anterior chamber: single incidences of flares G1 and 2 - none in G3-6
  - corneal cloudiness: single to minimal in all group-
  - corneal neovascularization: 1 instance in G6-
  - lens: 1 abnormality D148 in G1-
  - conjunctiva: low incidences of congestion, swelling, and discharge was seen in G1-5-  
congestion and discharge (no swelling) seen in G6-
  - fluorescein staining: single or low incidence in all groups-

- light reflex: no impairment in G1-5; 1 instance D30 in G6-
- indirect ophthalmoscopy: within normal limits for both eyes-

The condition of the eyes, as determined by biomicroscopic examination, was said to be within normal limits. All parameters were scored 0 except conjunctival congestion, which contained scores of 0 or +1 and were said to be acceptable.

- necropsy:

6-month sacrifice: N<sup>o</sup> G1(4♂5♀), G2(4♂5♀), G3(4♂4♀), G4(5♂6♀), G5(4♂4♂), G6(4♂5♀) - no treatment related changes-

12-month sacrifice: N<sup>o</sup> G1(8♂7♀), G2(8♂7♀), G3(8♂8♀), G4(8♂5♀), G5(8♂8♀), G6(8♂7♂) - no treatment related changes-

- histopathology: (6-Month Ocular Tissue)

- no adverse treatment related lesions in OD vs OS-
- other reported lesions were random and not treatment related-

- histopathology: (12-Month Ocular Tissue)

- no adverse treatment related lesions in OD vs OS-
- G1 1♂ suppurative meningitis and optic nerve suppurative perineuritis-
- G2 1♂ hyperplasia of corneal epithelium in treated eye-
- G4 1♂ hyperplasia of corneal epithelium in treated eye-
- other lesions noted were random and not treatment related-

- histopathology: (12-Month systemic)

• brain: multifocal areas of nonsuppurative encephalitis ♂(♀)

G1	G2	G3	G4	G5	G6
2/7(1/6)	1/6(3/6)	(1/5)	(2/5)	not examined	

• brain: microgranuloma

G1	G2	G3	G4	G5	G6
1/7	(3/6)		(1/5)	not examined	

• liver: congestion

G1	G2	G3	G4	G5	G6
4/7(2/6)	4/6(4/6)	5/7(3/5)	6/7(3/5)	7/7(5/7)	2/4(3/4)

• nasal cavity: suppurative rhinitis

G1	G2	G3	G4	G5	G6
3/6(3/6)	1/6(1/6)	5/7	5/7(2/5)	2/7(5/8)	1/4(2/4)

• nasal cavity: blood in lumen

G1	G2	G3	G4	G5	G6
2/6(1/6)	(1/6)	(1/5)		1/7(3/8)	

- electron microscopy: (6- and 12-month sacrifice, corneas only evaluated)

- G1 "The epithelial cells appeared normal. The membranes exhibited normal exfoliation holes as well as tight junctions and microvilli were normal in appearance."
- G2 "Much of the primary cell layer remained intact and exhibited normal junctions, microvilli and exfoliation holes. Minimal sloughing of cells was observed in isolated areas."
- G3 "The primary corneal epithelial cell layer remained largely intact. There was a normal number of exfoliation holes present and the microvilli appeared normal both in density and morphology."
- G4 "The primary corneal cell layer remained present, there was, however, some cell sloughing evident in isolated areas. Otherwise the microvilli, exfoliation holes, and tight junctions appeared normal."
- G5 "The primary corneal epithelial cell layer had sloughed exposing the underlying secondary and tertiary cell layers. There also appeared to be a loss of microvilli in isolated areas."
- G6 "The majority of the primary cell layer had sloughed exposing the underlying secondary cell layer. There was also evidence of junctional separation and pitting of the cell membranes."

## SUMMARY

Morbidity and mortality were excessive for this type of study. There was a 67%, 33%, 25%, 58%, 17%, and 75% mortality in G1 through G6, respectively. Deaths and moribund sacrifices were attributed to mucoid enteropathy, multifocal suppurative bronchopneumonia, bacterial/protozoal infections (*Pasteurella?*, *Encephalitozoon cuniculi*), or trichobezoar. In any case, mortality was excessive for this type of study.

Body weight showed a significant decrease (13% in females of the 0.001% thimerosal group. Only minimal ocular changes occurred in all groups. In addition, no systemic toxicity was produced by the treatment. The brain lesions were said to be compatible with *Encephalitozoon cuniculi* infections. Other lesions were kidney nephritis and liver pericholangitis, both were considered to be related to protozoan disease.

Table 7, p. 5-0771 (body wt) contains 11 males and 13 females for G5. The number of rabbits that died or were sacrificed in a moribund condition (Vol. 1.8, p. 5-1016) did not agree with what was indicated in Table 5, Vol. 1.7, p. 5-0695.

DICLOFENAC CONCENTRATIONS IN AQUEOUS HUMOR AND PLASMA FOLLOWING A SINGLE BILATERAL DOSE OF 0.1% DICLOFENAC OPHTHALMIC SOLUTION IN MALE NEW ZEALAND RABBITS:

Report N<sup>o</sup> 043:38570:0896, Vol. 1.8, pp.5-1245 to 5-1313

Compound: Diclofenac 0.1% Ophthalmic Solution, lot N<sup>o</sup> 95-12595

Formulation:

Diclofenac Sodium, NOC  
AL06778, NOC  
Mannitol, USP

Polyquaternium-1, NOC

HCl, NE/NaOH, NE  
Purified Water

0.1%

To adjust pH  
Qs to 100

Route: Ocular, topical

Dose Levels: 30 µL to both eyes

Strain: Male NZW, 2.99 ± 0.13 Kg

Number: 28 treated + 2 untreated

Study Site: Alcon Laboratories, Inc., Fort Worth, TX

Date: June 27, 1995 to September 1996

GLP/QAU Statements: Both present and signed.

Diclofenac concentrations were measured in the aqueous humor and plasma following a single bilateral dose of the 0.1% solution. Blood (≈ 5 mL) and aqueous humor (pooled from both eyes) was collected at 20, 40, 60 minutes, and at 2, 4, 6, and 8 hours. Aqueous humor and plasma samples were analyzed by CEDRA Corporation, Austin, TX. The limit of quantitation was 0.5 ng/mL for plasma and 5 ng/mL for aqueous humor.

## RESULTS

Mean Diclofenac Concentrations in Aqueous Humor and Plasma  
From Table 1, Vol. 1.8, p. 5-1251

TIME (Hr)	PLASMA (ng/mL)		AQUEOUS HUMOR (ng/mL)	
	Mean	Std. Dev.	Mean	Std. Dev.
0.33	27.6	6.4	44.0	26.2
0.67	20.2	7.4	84.4	12.3
1	15.8	4.2	146	83
2	8.46	3.4	106	41
4	3.17	1.04	53.3	6.9
6	0.70	0.05	25.8	10.0
8	BLQ		9.26	4.05

BLQ = below limit of quantitation (<0.5 ng/mL)

The half lives in plasma and aqueous humor were 1.1 and 2.0 hours, respectively. Individual animal plasma concentrations varied from 37.0 to 0.666 ng/mL, and the aqueous humor concentrations varied from 266 to 5.88 ng/mL.

DICLOFENAC PLASMA CONCENTRATIONS FROM TOXICOLOGY STUDY N-95-220: THREE MONTH TOPICAL OCULAR IRRITATION AND SYSTEMIC TOXICITY EVALUATION OF DICLOFENAC OPHTHALMIC SOLUTION IN RABBITS:

Report N° 035:38570:0796, Vol. 1.8, pp. 5-1314 to 5-1380

Formulation: See p. 4 for formulations of the following groups.

Group 3: 0.1% Diclofenac (0.016% BAB)

Group 5: 0.1% Diclofenac (0.005% Polyquad®)

Group 6: 0.1% Diclofenac (0.2% Sorbic acid)

Route: Ocular, topical

Dose Levels: 2 drops (≈ 70 µL) to OD qid

Strain: NZW, 2.0 to 3.5 Kg, 2-4 months of age

Number: 5/sex/group

Study Site: Alcon Laboratories Inc., Fort Worth, TX

Date: December 16, 1996

GLP/QAU Statements: Both present and signed.

Plasma samples were collected on D1, D30, D45, and D87 from 5/sex/group at 10 minutes prior to the last dose of the day to give the trough sample values and at 30 minutes after the last dose of the day to give peak sample values.

## RESULTS

The three formulations indicated systemic exposure to diclofenac, with no significant differences between male and female values. Mean plasma concentrations are indicated in the irritation and systemic toxicity study reviewed on page 3.

DISTRIBUTION OF RADIOACTIVITY IN OCULAR TISSUES FOLLOWING A SINGLE TOPICAL OCULAR DOSE OF 0.1% DICLOFENAC OPHTHALMIC SOLUTION CONTAINING 5% [<sup>14</sup>C-POLYETHYLENE GLYCOL 1000]-TOCOPHERSOLAN TO MALE NEW ZEALAND WHITE RABBITS:

Report N° 049:38570:1096

Compound: D- $\alpha$ -tocopherol-[<sup>14</sup>C]polyethylene glycol 1000 succinate, specific activity of 38.5  $\mu$ Ci/mg and radiochemical purity of 95%.

Route: Topical, ocular

Formulation: Solution containing [redacted] mannitol, [redacted] and [redacted] polyquaternium-1

Dose Level: Each single unilateral dose contained 1.5 mg of [<sup>14</sup>C-PEG]tocophersolan, 10  $\mu$ Ci

Strain: NZW,  $\approx$  3.3 Kg body weight

Number: 27 males treated + one undosed animal sacrificed for the collection of analytical control tissues for background.

Study Site: Alcon Laboratories, Inc., Fort Worth, TX

Date: October 21, 1996 to December 12, 1996

GLP/QAU Statements: Not present.

The study was done to quantify the distribution of radioactivity of [<sup>14</sup>C-PEG]tocophersolan in ocular tissues. Blood, plasma, aqueous humor, cornea, iris-ciliary body, lens, conjunctiva, and choroid were collected from three animals per time point at 0.5, 1, 3, 6, 10, 24, 48, 70, and 96 hours following dosing. The radioactivity was determined in the above tissues of each eye.

#### RESULTS AND DISCUSSION

Mean Concentrations of Radioactivity in Tissues Following a Single Topical Ocular Dose of 0.1% Diclofenac Ophthalmic Solution Containing 5% [<sup>14</sup>C-PEG]tocophersolan  
(From p. 5-1382)

TISSUE	C <sub>max</sub> ( $\mu$ g equivalents/g)	T <sub>max</sub> (Hr)	t <sub>1/2</sub> (Hr)
Aqueous Humor	0.0494 $\pm$ 0.0261	1	6.9
Cornea	0.436 $\pm$ 0.160	1	6.2
Iris-ciliary body	BLQ*	-	-
Lens	BLQ	-	-
Conjunctiva	1.72 $\pm$ 1.26	3	73
Choroid	BLQ	-	-
Blood	BLQ	-	-
Plasma	BLQ	-	-

\* BLQ = below quantitation limit - defined as 3 times below background ( $\approx$  30 dpm)

The radioactivity concentrations were below the assay quantitation limit in the lens, iris-ciliary body, choroid, plasma, and blood. Only the aqueous humor, conjunctiva, and cornea had detectable radioactivity - the highest being found in the conjunctiva. At 70 hours postdose, radioactivity was measurable in the OD conjunctiva of only one eye, but was measurable in five

of the samples at 96 hours. This was explained by the time of dosing and the nocturnal activity of rabbits, which allowed for increased grooming activity.

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**LABELING:**

The labeling for the Carcinogenesis, Mutagenesis, Impairment of Fertility section and the Pregnancy section are identical with the labeling for Voltaren Ophthalmic®, with the exception that the name Voltaren is replaced with diclofenac sodium.

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**SUMMARY AND EVALUATION:**

This NDA was submitted under the provisions of Section 505(b)(2). Alcon developed Diclofenac Sodium Ophthalmic Solution 0.1% for treating postoperative inflammation after cataract surgery. The formulation is similar to Ciba Vision Ophthalmics' approved Voltaren Ophthalmic 0.1% Sterile Solution (diclofenac sodium) for the same indication. Alcon's product contains 0.005% polyquaternium-1, a preservative [redacted]

Polyquaternium-1 is approved in contact lens products and as a preservative in Alcon's TEARS NATURALE®, in OPTI-TEARS® Soothing Drops, and in other approved products. Alcon stated that Tocophersolan has been evaluated by the NCI in a one year oral toxicity study in rats and dogs. Dose levels were 100, 300, and 1000 mg/Kg/day. No treatment-related effects were said to have been "elicited" (Vol. 1.1, p. 2-0029).

Submitted pharmacology/toxicology studies included an evaluation of the proposed clinical formulation of diclofenac containing vitamin E TPGS, two three-month topical ocular irritation and systemic toxicity studies in rabbits, and a one-year chronic topical ocular irritation evaluation of Polyquad in rabbits, the preservative used in their formulation.

The two three-month topical ocular irritation and systemic toxicity studies were conducted with four 0.1% diclofenac sodium ophthalmic formulations. None of the formulations were identical to the proposed formulation of the drug product; however, two formulations contained 0.001% polyquad and [redacted] tocophersolan. A 0.2% diclofenac ophthalmic solution was also evaluated in one of the studies. Voltaren Ophthalmic 0.1% Sterile Solution was included in one of these studies for comparison. Gross observations included sporadic changes in all groups, including controls. Microscopic evaluation of the eyes, adnexa, and nasal lacrimal tissues and pachymetry measurements of the eyes did not show findings related to drug treatment. The histopathology findings reported in these studies did not indicate any systemic toxicity.

The one-year topical ocular irritation evaluation of polyquad was conducted in rabbits with 0.001%, 0.01%, and 0.05% concentrations. These polyquad concentrations were compared with 0.001% thimerosal and 0.01% benzalkonium chloride, two other preservatives used in other ophthalmic formulations. Minimal ocular changes were produced in all groups in the study. No adverse treatment-related lesions were reported in the treated eyes (OD) when compared to the untreated eye (OS). [redacted] evaluations at six and twelve months indicated normal corneal epithelium in the polyquad treated eyes. There was some sloughing of primary epithelial cells in

isolated areas in the 0.05% polyquad group, which was reported as reversible. These changes were less severe than those changes reported in the thimerosal and benzalkonium chloride treated eyes. No systemic toxicity was produced by the treatment.

Pharmacokinetic data derived from a single bilateral topical ocular administration of 0.1% diclofenac solution to rabbits indicated a half-life of 1.1 hours in blood plasma and 2 hours in aqueous humor. The highest value in the aqueous humor was 146 ng/mL, which occurred at 1 hour. Systemic exposure to diclofenac was demonstrated, with no significant difference between the sexes. Plasma levels were below the quantitation limit of <0.5 ng/mL eight hours after drug application - aqueous humor levels were at 9 ng/mL.

Ocular distribution of 5% [<sup>14</sup>C-polyethylene glycol 1000]-tocophersolan in 0.1% diclofenac ophthalmic solution administered to male rabbits indicated radioactivity in the aqueous humor, cornea, and conjunctiva. Other ocular tissues, blood, and plasma did not have measurable levels of <sup>14</sup>C over 96 hours. The terminal half-life in the conjunctiva was 73 hours.

#### RECOMMENDATIONS:

There are no pharmacology-toxicology objections to the approval of this NDA. Request Alcon to submit a summary of the one year tocophersolan study evaluated by NCI.



Almon W. Coulter, Ph.D.



Team Leader: Conrad Chen, Ph.D.

3-7-97

#### cc:

NDA 20-809

HFD-550/Division File

/CSO JHomes

/Pharmacol. ACoulter

/MO ELudwig

HFD-345

F/T by AWC 2/28/97

THE DIVISION OF ANTI-INFLAMMATORY, ANALGESIC,  
AND OPHTHALMIC DRUG PRODUCTS

PHARMACOLOGY/TOXICOLOGY REVIEW  
REVIEW N<sup>o</sup> 2

**NDA 20-809**                      Amendment

**DRUG:**                              Diclofenac Sodium Ophthalmic Solution 0.1%

**SPONSOR:**                         Alcon Laboratories, Inc.  
Fort Worth, Texas 76134

**REVIEWER:**                        A. W. Coulter, Ph.D.

**SUBMISSION DATE:**                March 13, 1997

**REVIEW COMPLETED:**            April 30, 1997

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**PRECLINICAL STUDIES:**

We requested Alcon to submit summary data on the one year tocophersolan study evaluated by NCI. This amendment contains the complete NCI study and other studies that have been done with tocophersolan. Included in this three volume amendment are the following:

- a) One Year Chronic Oral (Intubation) Study in Dogs.
- b) One Year Chronic (Intubation) Study in Rats.
- c) [redacted] Mutation Assay With an Independent Repeat Assay With Tocophersolan.
- d) [redacted] Assay in Mice With Tocophersolan.
- e) A Summary of Studies Conducted [redacted]
  - Study Report #1. Acute Oral Toxicology of [redacted] to Mature and Neonatal Rats.
  - Study Report #2. D-Alpha-Tocopherol Polyethylene Glycol Succinate, Subchronic Feeding, Reproduction and Teratology Studies in Rats.
  - Study Report #3. The Physiological Activity of d-Alpha-Tocopherol Polyethylene Glycol 1000 Succinate (Tocopherol PGS).

**Abbreviations Used In This Review**

D = day(s)      DR = dose related      G = group(s)      M = month(s)      W = week  
 \* = p<0.05      \*\* = p<0.01      ↑ = increase or elevated      ↓ = decrease or reduced  
 ♂ = male(s)      ♀ = female(s)

**ONE YEAR CHRONIC ORAL (INTUBATION) STUDY IN DOGS.**Report N<sup>o</sup>: Study N<sup>o</sup> 560-041Compound: Vitamin E TPGS (EASTMAN®), lot/batch N<sup>o</sup> AA26-1191  
(d-alpha tocopherol polyethylene glycol 1000 succinate)  
purity 100%

Formulation: Solution in deionized water.

Route: Oral, gavage

Diet: *Ad libitum*

Strain: Beagle, body weight ♂ 7.9-11.9 Kg, ♀ 6.7-11.5 Kg

Dose Levels: Group:	1	2	3	4	
mg/Kg/day:	0	100	300	1,000	for 52 weeks
mL/Kg:	10	10	10	10	

Number: 4/sex/group

Control Treatment: Deionized water

Study Site: 

Date: August 4, 1992 - November 4, 1994

GLP/QAU: Both present and signed.

The purpose of the study was to determine the chronic toxicity of  when administered daily to dogs for one year.

The animals were observed at least twice daily for clinical signs and mortality. Body weights were recorded pretest and weekly. Food consumption was measured weekly. Ophthalmoscopic examinations were conducted pretest and at 3, 6, 9, and 12 months. Leads I, II, III, AVR, AVL, and AVF EKGs were recorded on each dog once during the pretest and at 1, 3, 6, and 9 months. Hematological, biochemical, and urinalysis were conducted on 20/sex prior to initiation and on all surviving animals at 3, 6, 9, and 12 months. Blood samples were collected 3 hours post dose from 3/sex/group at 3, 6, 9, and 12 months for evaluation of alpha-tocopherol. All animals received gross and microscopic examinations. Brain, adrenal, heart, kidney, liver, pituitary, spleen, testis, and thyroid/parathyroid weights were recorded.

At W8 two G3 ♂ were placed on study to replace two that died or were submitted for euthanasia due to possible gavage errors. Data for these animals are not included in the report but are retained in the files.

**RESULTS AND DISCUSSION**

- mortality: 2♂G3 submitted for euthanasia due to possible gavage error-  
1♂G4 found dead D212 - red material in cage at time of death-  
1♀G4 sacrificed in extremis D347 - dark feces, decreased activity, ptyalism, decreased defecation, prior to sacrifice-
- observed effects: decreased activity (1G4♂, 1G2♀)-  
tremors (2G4♂, 1G3♀, 1G4♀)-  
trembling (2G3♀)-  
emesis (all groups)-  
frothy emesis (all groups)-  
increased respiratory rate (1G4♂)-  
labored breathing (1G3♂)-  
ptyalism (1G4♂)-  
prostration (1G4♀)-
- body weight: no significant changes from control-
- food consumption: slight ↓ in ♂ and ♀ G2 and G3 - not significant-
- ophthalmoscopic examination: no unusual findings reported-
- EKGs: all animals were said to be within normal limits (no hard data)-
- hematology: ↓ platelets ♂G2 M6(\*, 27%), M12(\*, 36%); ♂G4 M6-12 (\*, 32-43%)-

- clinical chemistry: some parameters significant at times but not DR-
- urinalysis: no significant changes in volume, specific gravity, or pH-
- gross pathology: changes were considered to be spontaneous/incidental-
- organ weights: ↓ mean relative kidney/brain weight G2 (\*\*, 21%)-
- histopathology:
  - 1 of the two G4 animals that died or was sacrificed had acute bronchopneumonia and the other was diagnosed with chronic active pyelonephritis-
- plasma analysis: (results in  $\mu\text{g/mL} \pm \text{S.D.}$ )

Summary of Mean Alpha-Tocopherol in Dog Plasma  
(From Vol. 3.1, p. 00034)

Dosage (mg/Kg/day )		3-Months	6 Months	9 Months	12 Months
0	♂	1.008±0.1467	2.0819±2.2678	4.1089±1.3790	1.6266±1.6101
	♀	0.9969±0.6913	4.3483±1.5322	2.7263±0.7258	3.5611±2.0906
100	♂	9.5380±5.0035	5.5260±1.1222	10.5860±1.4868	9.6740±1.0730
	♀	10.4798±3.8192	7.1838±4.2146	7.7017±3.4715	11.7752±0.4435
300	♂	16.0013±3.7260	6.5148±3.2239	7.0272±2.8013	5.1137±1.4272
	♀	15.9817±1.5209	7.9504±4.2542	12.4793±1.8493	8.9784±4.4144
1000	♂	14.3037±4.1565	8.2269±4.3672	13.5899±1.0930	12.6081±1.0781
	♀	11.1652±1.8387	10.6971±2.0273	10.8296±2.7871	15.9348±5.4368

The administered dosage was reduced during episodes of emesis, as test material was verified in the expelled emesis. Platelets showed a DR decrease in males and was significant at  $p < 0.05$  in G2 to G4. Other clinical chemistry parameters differed significantly from controls at times, but no consistent DR changes were noted. Microscopic changes that occurred were not treatment related. In the two dogs that died, the high dose male was observed with bronchopneumonia and multifocal hemorrhage, lymph node necrosis (mild/moderate), and tonsil necrosis (mild), with the cause of death attributed to bronchopneumonia. The other high dose animal sacrificed moribund was observed with chronic/active/diffuse/severe pyelonephritis, multifocal/mild lung congestion, and pneumonia, with the cause of death attributed to pyelonephritis. The study director did not consider these deaths to be treatment-related. Two replacement animals were added to the study on W8.

#### ONE YEAR CHRONIC ORAL (INTUBATION) STUDY IN RATS.

Report N<sup>o</sup>: [redacted] Study N<sup>o</sup> 560-040

Compound: [redacted]  
(d-alpha tocopherol polyethylene glycol 1000 succinate)

Formulation: Solution in deionized water.

Route: Oral, gavage

Diet: *Ad libitum*

Strain: [redacted] CD<sup>o</sup>, 4 weeks old, body weight ♂ 169-208 g, ♀ 132-154 g

Dose Levels: Group: 1      2      3      4  
 mg/Kg/day: 0      100      300      1,000 for 52 weeks  
 mL/Kg: 10      10      10      10

Number: 25/sex/group

Control Treatment: Deionized water

Study Site:

Date: August 13, 1992 - November 1, 1994

GLP/QAU Statements: Both present and signed.

The purpose of this study was to evaluate the chronic toxicity of Vitamin E TPGS when administered daily to rats for one year.

Observation of the animals was twice per day for mortality, morbidity, and for toxic signs. Body weight was recorded pretest and weekly thereafter. Food consumption was measured weekly. Ophthalmoscopic examinations were conducted pretest and at 6 and 12 months. Hematology, clinical chemistry, and urological parameters were determined on 10 randomly selected animals per sex per group at 3, 6, 9, and 12 months. Blood was collected from 5/sex/group about 3 hours post dosing at 3, 6, 9, and 12 months for determining plasma levels of Vitamin E TPGS. Gross examinations were done on all animals. Histopathology was conducted on all animals in the control and high dose groups. Gross lesions and tissue masses were also examined microscopically. Absolute and relative organ weights were recorded.

#### RESULTS AND DISCUSSION

- 1G1 ♂ and 1G2 ♂ sacrificed in extremis-
- found dead:
 

G1	G2	G3	G4
3♂	4♂, 1♀	4♂, 2♀	8♂, 2♀
- no DR clinical signs-
- no significant changes in ♂♀ body weight-
- food consumption showed a significant increase at times in treated groups-
- ophthalmic examinations did not reveal test article-related abnormalities-
- Hb and Hct values ↓ (\*, 6-10%) in ♀ G2 and G4 on occasion-
- no biological significant changes in clinical chemistry-
- urine specific gravity ↑ ♂G4 at termination (\*, 0.68%)-
- gross observations were not DR and were considered spontaneous-
- kidney/brain weight significantly ↑ in ♂G2 (\*, 10%) and ♂G4 (\*, 11.7%)-
- microscopic lesions in the high dose group were not DR-
  - 1♀G4 died on study with astrocytoma-
  - 1♂G4 brain hemorrhage (trace)-
  - 1♂G4, 1♀G2 liver necrosis, coagulative (trace)-
  - 1♂G4 severe aspermia-
  - 2♂G4 mild cataracts-
- plasma analysis

Summary of Mean  in Rat Plasma  
( $\mu\text{g/mL} \pm \text{S.D.}$ )  
From Vol. 3.2, p.00439

Dose (mg/Kg/day)		3 Months	6 Months	9 Months	12 Months
0	♂	0.861	0.291	0.352	0.866±0.871
	♀	0.961	1.476±1.001	0.454±0.510	1.397±0.352
100	♂	1.177	2.359±1.832	0.490±0.208	1.343±0.855
	♀	2.029±1.390	7.230±2.299	1.298±0.837	2.884±1.341
300	♂	2.644±1.360	4.187±3.169	0.804±0.329	1.713±1.401
	♀	2.858±1.119	4.644±3.737	1.551±1.549	2.896±2.034
1000	♂	8.550±2.388	4.940±4.528	1.095	3.004±2.948
	♀	5.470±1.126	6.815±3.479	1.428±0.227	2.162±0.465

Deviations from the protocol included, among other things, the purity and shelf life/expiration for the 10951B test article were not available. The study did not produce any DR toxicity; however, mortality appeared to be treatment related (3, 5, 6, 10 in G1, G2, G3, and G4, respectively). Deaths in the control were certainly due to gavage errors; in the compound treated groups, some of the mortality may also be associated with gavage error. The cause of death for these animals was not indicated for all, but some, although not stated, were from intubation errors.

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**MUTATION ASSAY WITH AN INDEPENDENT REPEAT ASSAY WITH TOCOPHERSOLAN.**

Report N° TR 155:38520:1196

The potential for tocophersolan [redacted] to cause base pair changes or frameshift mutations was evaluated in [redacted] tester strains. The study was evaluated in the presence and absence of [redacted] induced rat liver

Under the conditions used in these assays, tocophersolan did not produce a positive response in the number of revertants per plate, with or without Positive controls produced at least a three-fold increase in the number of revertants over the mean value of the respective vehicle control. Date of study was August 21, 1996 - January 6 1997

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**ASSAY IN MICE WITH TOCOPHERSOLAN.**

Report N° TR 156:38520:1196

This study evaluated the potential of tocophersolan to increase micronucleated polychromatic erythrocyte stem cells in bone marrow of male and female mice.

[REDACTED]

In the repeat [REDACTED] assay, no mortality occurred. Lethargy was seen at 310 mg/Kg the days following dose administration. Under the conditions of the assay, tocophersolan did not increase the incidence of micronucleated polychromatic erythrocytes in bone marrow harvested at any collection time in either sex. Cyclophosphamide significantly increased the incidence of micronucleated polychromatic erythrocytes.

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**SUMMARY OF STUDIES CONDUCTED** [REDACTED]  
Study Report #1 (dated March 1976)

**ACUTE ORAL TOXICOLOGY** [REDACTED] **TO MATURE AND NEONATAL RATS.**

[REDACTED] polyethylene glycol 1000 (PG 1000), and d-alpha tocopheryl acid succinate NF (DTS) were evaluated for acute toxicity. Ten male and female rats per group were intubated at 7000 mg/Kg of each of the three compounds dissolved in corn oil. Gross necropsy was performed on all animals. No corn oil control was included in the study.

**Mature Rats:** Following replacement of the 5 animals that died within 24-48 hours, all replacements survived the study. Intubation errors were assumed to be the cause of death. All survivors gained weight, and no gross changes in behavior, stool, or coat were noted. Lassitude and diarrhea was seen during the first 24 hours.

**Neonates:** The groups were intubated at 0.075, 0.10, and 0.15 mL/pup with DTS, TPGS 1000, PG 1000, and corn oil. Concentrations were not indicated for the solutions. Doses were not measured on a mg/Kg basis. Pups were observed daily and weighed at 3, 10, and 17 days after intubation. The results indicated a DR increase in mortality with the three treated male groups and with females in the DTS group. Mortality from corn oil appeared to be erratic between males and females. It is not known what percent of the animals died from intubation errors. Mortality was roughly similar between DTS, TPGS 1000, and PG 1000.

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Study report #2 (dated March 1976).

**D-ALPHA-TOCOPHEROL POLYETHYLENE GLYCOL SUCCINATE, SUBCHRONIC FEEDING, REPRODUCTION, AND TERATOLOGY STUDIES IN RATS.**

THE Data was limited to half a page in this report. Toxicity was evaluated in a feeding study in which albino rats were dosed at 0.002, 0.2, and 2.0% of the diet for 91 days. It was said no adverse effects on the general appearance and behavior, feed consumption, or growth rate occurred.

Blood chemistry, hematology, organ weights, and microscopic examination of tissues from "all organ systems" (no data given) were indicated as being normal.

Reproductive indices and offspring were said to be comparable to controls, and microscopic examination of tissue from parents and offspring were said to show no pathology due to ingestion of the compound. Fetuses collected from the organogenesis period were indicated as having no congenital abnormalities which could be attributed to the compound.

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### Study Report # 3.

This report contains short summaries from studies conducted in 1959. These studies included: a) Antisterility Potency by Standard Bioassay Procedure, b) Acute Toxicity by Oral Administration in Rats, c) Acute Toxicity by IM Injection in Rats, and d) Acute Toxicity by IP and SQ Injection in Rats.

No gross effects were reported in animals dosed orally with aqueous solutions of 0.025 to 4 g/Kg of TPGS. Fifty percent mortality of half of the orally treated rats was >4.0 g/Kg. The irritation effects were slight following the injection of a 15% aqueous solution in the hind leg muscle of 10 adult male rats - absorption was rapid, and muscle recovery required 6 to 12 days. IP administration in adult rats with 15% and 25% aqueous solutions produced median lethality at 48 hours. Orally administered tocopherol PGS was found to be more efficiently utilized than when administered by injection.

### SUMMARY AND EVALUATION:

Little toxicity was observed in the rat and dog oral gavage study. Treatment was at 100, 300, and 1000 mg/Kg/day in both species, with 4/sex/group in the dog study and 25/sex/group in the rat study. Both studies were carried out [redacted]

Two high dose dogs died on study, one from bronchopneumonia, the other from pyelonephritis. Mortality in rats was dose related (3, 5, 6, 10) and appeared to be treatment related; the cause of death, however, was not apparent for all animals. Some of the deaths may have been caused by intubation errors.

The [redacted] mutation assay [redacted] and the [redacted] assay in mice were both negative. Summary studies that were included in this submission were done in 1976 but did not contribute much to the overall toxicity profile for tocophersolan.

All in all, tocophersolan is an excipient that can be considered to be nontoxic at the concentration that will be used in Diclofenac Sodium Ophthalmic Solution 0.1%.

[Redacted signature]

Almon W. Coulter, Ph.D.

[Redacted signature] 5-6-97

Team Leader: Conrad Chen, Ph.D.

CC:  
NDA 20-809  
HFD-550/Division File  
/P/T ACoulter  
/CYaciw  
/ELudwig  
/DGunter  
F/T by AWC 4/30/97