NDA 19-404

APPROV.
LETTER

DEC 31 1986

NDA 19-404

Mr. William Fairbairn
Allergan Pharmaceuticals
2525 Dupont Drive
Irvine, CA 92715

Dear Mr. Fairbairn:

Reference is made to your New Drug Application (NDA) dated December 14, 1984 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ocufen (flurbiprofen) Ophthalmic Solution, 0.03%.

We also acknowledge receipt of your additional communications dated January 30, June 4, July 15, August 2, November 8, November 11, 1985, March 4, June 24, and December 11, 1986.

We also acknowledge the December 17, 1986 telephone conversation between Mr. Robert Linkous and yourself during which you agreed with the labeling revision listed below.

We have completed the review of this application including the submitted draft labeling dated December 11, 1986 and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted draft labeling as revised below. Accordingly, the application, with the labeling revisions described below, is approved effective as of the date of this letter.

The labeling revisions are as follows:

In the Clinical Pharmacology section, the phrase, "in human and animal inflammatory diseases" should read: "in animal inflammatory diseases."

In the Precautions sections, "Pregnancy category C:"should be replaced with "Pregnancy: Pregnancy category C:".

In the first paragraph of the Adverse Reactions section, change the word "signs" to the word "symptoms."

The Dosage and Administration section should read:

"A total of four drops of Ocufen should be administered by giving one drop approximately every half hour beginning two hours before surgery."

Please submit twelve copies of the revised final printed labeling (FPL) when it is available. This submission should be designated as "FPL Supplement" to the approved NDA 19-404. Approval of the supplement by the Food and Drug Administration is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of this drug product become available, further revision of that labeling may be required.

In addition, please submit, in duplicate, all advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Anti-Infective Drug Products, and the second copy to the Division of Drug Advertising and Labeling, HFN-240, Room 10B-04, 5600 Fishers Lane, Rockville, Maryland 20857.

Please submit one market package of the drug when it is available.

We remind you that must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

for JBilstad 12/31/86

Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

cc: LOS-DO
ORIG. NDA 19-404
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See attached cartons for supervisors' signatures (initials). Retyped to correct signature block.

LBLING

Ocufen™

(flurbiprofen sodium) 0.03%

Liquifilm®

sterile ophthalmic solution

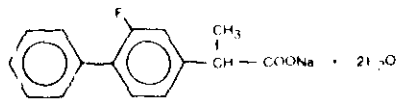
ALLERGAN®

DESCRIPTION

Ocufen (flurbiprofen sodium) 0.03% Liquifilm sterile ophthalmic solution is a topical *nonsteroidal* anti-inflammatory product for ophthalmic use.

Chemical Name:
Sodium (±)-2-fluoro-α-methyl-4-biphenylacetate dihydrate.

Structural Formula:



flurbiprofen sodium

Contains:
flurbiprofen sodium 0.03%
with: Liquifilm® (polyvinyl alcohol) 1.4%; thimerosal 0.005%; edetate disodium; potassium chloride; sodium chloride; sodium citrate; citric acid; hydrochloric acid and/or sodium hydroxide to adjust the pH; and purified water.

CLINICAL PHARMACOLOGY

Flurbiprofen sodium is one of a series of *phenylalkanoic acids* that have shown analgesic, antipyretic, and anti-inflammatory activity in animal inflammatory diseases. Its mechanism of action is believed to be through inhibition of the cyclo-oxygenase enzyme that is essential in the biosynthesis of prostaglandins.

Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed on animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilatation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

Prostaglandins also appear to play a role in the miotic response produced during ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms. In clinical studies, Ocufen has been shown to inhibit the miosis induced during the course of cataract surgery. *Ocufen does not interfere* with the miotic effect of intraoperatively administered acetylcholine chloride.

Results from clinical studies indicate that flurbiprofen sodium has no *significant effect* upon intraocular pressure.

INDICATIONS AND USAGE

Ocufen is *indicated for the inhibition of intraoperative* miosis.

CONTRAINDICATIONS

Ocufen is contraindicated in epithelial herpes simplex keratitis (*dendritic keratitis*) and in individuals who are hypersensitive to any components of the medication.

WARNINGS

There exists the potential for cross sensitivity to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

PRECAUTIONS

General: Patients with histories of herpes simplex keratitis should be monitored closely. Ocufen™ (flurbiprofen sodium) 0.03% Liquifilm® sterile ophthalmic solution is contraindicated in patients with active herpes simplex keratitis.

Wound healing may be delayed with the use of Ocufen.

Drug interactions: Interaction of Ocufen with other topical ophthalmic medications has *not been fully investigated.*

Carcinogenesis, mutagenesis, impairment of fertility: Long term studies in mice and/or rats have shown no evidence of carcinogenicity or impairment of fertility with flurbiprofen.

Long term mutagenicity studies in animals have not been performed.

Pregnancy:
Pregnancy category C. Flurbiprofen has been shown to be embryocidal, delay parturition, prolong gestation, *reduce weight, and/or slightly retard growth of fetuses when given to* rats in daily oral doses of 0.4 mg/kg (approximately 185 times the human daily topical dose) and above. There are no adequate and well-controlled studies in pregnant women. Ocufen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers: *It is not known whether this drug is excreted in human milk. Because* many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from flurbiprofen sodium, *a decision should be made* whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use: *Safety and effectiveness in children have not been established.*

ADVERSE REACTIONS

The most frequent adverse reactions reported with the use of Ocufen are transient burning and stinging upon instillation and other minor symptoms of ocular irritation.

It is known that some systemic absorption does occur with ocularly applied drugs, and that nonsteroidal anti-inflammatory drugs have been shown to increase bleeding time by interference with thrombocyte aggregation. However there have been no reports that ocularly applied Ocufen affects bleeding time. It is recommended that Ocufen be used with caution in patients with bleeding tendencies.

OVERDOSAGE

Overdosage will not ordinarily cause acute problems. If accidentally ingested, drink fluids to dilute.

DOSAGE AND ADMINISTRATION

A total of four (4) drops of Ocufen should be administered by instilling 1 drop approximately every ½ hour beginning 2 hours before surgery.

HOW SUPPLIED

Ocufen (flurbiprofen sodium) 0.03% solution is supplied in plastic dropper bottles in the following sizes:

2.5 mL—NDC 11980-801-03
5 mL—NDC 11980-801-05
10 mL—NDC 11980-801-10

Note: Store at room temperature.

Caution: Federal law prohibits dispensing without prescription.

December 1986

ALLERGAN AMERICA, Hormigueros, Puerto Rico 00660
Printed in U.S.A.

PR 7727 31-12/H

MED REVIEW

Medical Officers Review of NDA 19,404

Date: May 20, 1985

Sponsor: Allergan Pharmaceuticals, Inc.
2525 Dupont Drive
Irvine, California 92715

Name of Drug: Flurbiprofen Ophthalmic Solution

Pharmacologic Category: Non-Steroidal Anti-inflammatory

Dosage Form and Route of Administration: 0.03% solution for topical ophthalmic administration.

Proposed Indication: Treatment of non-infectious inflammatory conditions of the eye.

Manufacturing Controls: Refer to chemistry review

Pharmacology: Flurbiprofen is a member of the phenylalkanoic acid series. Like its parent compound ibuprofen, flurbiprofen is a non corticosteroidal anti-inflammatory agent with analgesic and anti-pyretic activity. An important property of this class of drugs is their ability to interfere with prostaglandin synthesis through inhibition of the enzyme cyclo-oxygenase. Flurbiprofen is a particularly potent inhibitor of this enzyme.

The topical activity of flurbiprofen was assessed in three models: experimental immunogenic uveitis, endotoxin induced inflammation and a reverse arthus model of inflammation.

1. Experimental Immunogenic Uveitis: Several models were studied, the most important comparing flurbiprofen to prednisolone. Flurbiprofen was ineffective in the treatment of uveitis at 0.01%, but 0.03% gave statistically similar results to 0.12% prednisolone, as did 0.1% flurbiprofen to 1% prednisolone. Flurbiprofen is, therefore, equally effective against this form of anterior uveitis as prednisolone at a log unit lower dosage.

2. Endotoxin Induced Inflammation: Endotoxin induced breakdown of the ocular blood aqueous barrier was used as a model to quantitate the ocular anti-inflammatory activity of flurbiprofen. Fluorescein isothiocyanate labeled dextran leakage into the anterior chamber after IV administration was measured non-invasively with a coherent fluorophotometer. A dose response series was done with 0.01, 0.03, 0.1% sodium flurbiprofen. The percent inhibition of FITC-dextran leakage was 36 $\pm$ 9, 63 $\pm$ 9, and 82 $\pm$ 4 respectively.

3. Reverse Arthus Reaction Model of Inflammation. This model was used to determine the topical efficacy of flurbiprofen in allergic induced inflammation. The time course of Fluorescein isothiocyanate labeled dextran accumulation was similar to the endotoxin model.

The percent inhibition by 0.03% flurbiprofen was 37 ± 10, 72 ± 6, 66 ± 13 and 71 ± 7 at 30, 60, 90 and 120 minutes respectively. A comparison was also made with 1% indomethacin and there was no statistically significant difference in the anti-inflammatory action curves of flurbiprofen and indomethacin.

Flurbiprofen, 0.1% applied topically in one eye in 9 albino rabbits, produced no increase in intraocular pressure during 18 days of q. i. d. treatment. The same rabbits did respond with a pressure rise when treated with 1.0% prednisolone acetate according to the same treatment regimen.

Flurbiprofen, at concentrations of 0.01%. 0.03%, and 0.1% significantly decreased in a dose-dependent manner, the rate of vessel growth compared to vehicle controls in both silver nitrate cauterization and anterior chamber alloxan models of corneal neovascularization. Prednisolone 1% inhibited neovascularization in the latter model, but was ineffective in the former. The mechanism is unknown, but is likely to be via inhibition of prostaglandin formation and/or inhibition of leukocyte infiltration. Possibly related to inhibition of neovascularization are the significantly lower corneal wound strengths that have been demonstrated in flurbiprofen treated rabbit corneas.

Flurbiprofen is devoid of glucocorticoid activity and its specific actions are not mediated by the adrenal cortex. Also, it has no estrogenic or anti-estrogenic activity.

Toxicology:

Carcinogenicity: Flurbiprofen was administered in the diet for 80 weeks to groups of 50 male and 50 female CFLP mice at dose levels of 2, 5 and 12 mg/kg daily. There was no significant effect on the survival or health of the mice, except weight gain of males on 12 mg/kg daily was slightly depressed. The number of tumor bearing animals was similar among flurbiprofen treated and control mice, and there was no treatment related effect on the tumor type, frequency or time of onset. It was concluded, therefore, that flurbiprofen has no carcinogenic potential in the mouse.

Reproduction Studies:

1. Flurbiprofen slightly retarded fetal growth of Boots-Wistar rats dosed orally with 25 mg/kg daily from day 1 to 20 of pregnancy. This dose was ulcerogenic to the dams, resulting in the deaths of a few and retardation of growth in others, some of which had intrauterine hemorrhage.

2. Flurbiprofen administered orally to Boots-Wistar rats at dose levels of 0.675, 2.25, 7.5 or 25 mg/kg daily from day 1 of pregnancy to labor caused a prolongation of pregnancy with uterine hemorrhage and death of the dams in labor, an increase in stillbirths and reduction in litter survival. The drug was ulcerogenic to the gastrointestinal tract of the dam given 7.5 mg/kg daily or more, and possibly at 2.25 mg/kg.

3. Flurbiprofen, in a dosage of 0.674, 2.25, or 7.5 mg/kg daily, administered orally to New Zealand white rabbits from day 1 to 29 of pregnancy, was not embryotoxic ot teratogenic. All three dose levels were ulcerogenic to the dams, resulting in a few deaths at the highest level.

Eye Topical Studies: Female New Zealand Albino rabbits receiving multiple topical instillations of 0.03%, 0.1%, and 1.1% flurbiprofen for one day showed slight to moderate discomfort following instillation at the 0.1% and 1.1% concentrations. No toxic ocular reactions occurred at any of the three concentrations tested. Treatment with 0.03%, 0.10% and 0.30% flurbiprofen at a rate of one drop twice daily for one year produced no solution related effects.

Clinical Background: Flurbiprofen is currently used in many countries in an oral form to treat such as rheumatoid arthritis and ankylosing spondylitis. However, a topical ophthalmic formulation has not yet been marketed for clinical use.

Literature References:

1. Cohen, R.D. et al. Near-fatal bronchospasm in an asthmatic patient following ingestion of flurbiprofen - A case report. S. African Med. J. 1982 May 22; 61 (21); 803.

Reported is a case of a 42 year old women with mild asthma who had a near-fatal attack of bronchospasm and required intermittent position pressure vastilation and resuscitation following ingestion of a single tablet of flurbiprofen. The authors feel that the patients with asthma should receive a small test dose and administration of the first dose under supervision.

2. Gieser, D.K. et al. Flurbiprofen and intraocular pressure. Ann Ophthal 1981 June; 13 (7): 831-3.

Doubled masked testing of flurbiprofen in known corticosteroid responders did not alter intraocular pressure nor did it block corticosteroid-induced ocular hypertension.

3. Hotchkiss, M.L. et al. Nonsteroid anti-inflammatory agents after argon laser trabeculoplasty: A trial with flurbiprofen and indomethacin. Ophthalmology 1984 Aug; 91 (8): 969:76.

Seventy glaucomatous eyes received argon laser trabeculoplasty (ALT) to 180 degrees of the trabecular meshwork. Thirty six eyes were treated with topical .03% sodium flurbiprofen; 34 eyes received placebo. Eyes treated with flubiprofen showed significantly less conjunctival injection following ALT, but the anterior chamber reaction was not significantly altered. Treated eyes showed a significantly smaller percent (32.6%) decrease in intraocular pressure one day after ALT was compared to eyes receiving placebo (43.8%). In addition, a higher percentage of placebo treated eyes had a fall in IOP of at least 10mm Hg up to five weeks after ALT. Mild ocular symptoms (itching, burning, foreign body sensation) developed in 77.0% of flurbiprofen treated eyes, but only in 20.9% of eyes receiving placebo.

Clinical Studies:

I. Control of Ocular Inflammation After Cataract Surgery

A. Protocol No. FLUR-130/919-5827

Title: The Efficacy and Safety of Flurbiprofen in Inhibiting Ocular Inflammation after Intracapsular Cataract Extraction.

Investigators: David Sabiston, M.D., D.O.
Napier P.O. Box 294
Hawkes Bay, New Zealand

Howard Tessler, M.D.
Illinois Eye and Ear Infirmary
1855 W. Taylor Street
Chicago, Illinois 60612

Study Objective: To evaluate the efficacy and safety of 0.03% flurbiprofen ophthalmic solution compared with vehicle in inhibiting ocular inflammation after intracapsular cataract extraction.

Study Design: Two week double masked, randomized, parallel group clinical trial.

Number of Subjects: 72 evaluated for efficacy from an original group of 80, eight of whom were disqualified. Three of these (one on flurbiprofen and two on vehicle) had a significant post-operative iritis requiring other therapy. The other 5 were disqualified for administrative reasons.

Study Results: There were no statistically significant differences between the two treatment groups in demographic variables or medical and ophthalmologic histories. The treatment results were tabulated separately for four major variables:

1. Conjunctival Injection: Mean severity was less in the flurbiprofen group than in the vehicle group throughout the study, and the difference was significant on Day 14 (see sponsors Table 5).

Table 5 - CONJUNCTIVAL INJECTION

Day	Treatment	Severity* n	0	1	2	3	Mean Change From Baseline	SD	Within-Group p-value	Between-Group p-value
-3 (baseline)	FLUR	36	36	0	0	0	---	---	---	NS
	VEH	36	35	1	0	0	---	---	---	
3	FLUR	36	0	15	20	1	1.6	0.5	0.001	NS
	VEH	36	0	13	17	6	1.8	0.7	0.001	
7	FLUR	35	1	21	11	2	1.4	0.7	0.001	NS
	VEH	35	1	18	14	2	1.5	0.7	0.001	
14	FLUR	34	3	26	5	0	1.1	0.5	0.001	0.001
	VEH	34	3	10	19	2	1.6	0.7	0.001	

*0 = none, 1 = mild, 2 = moderate, 3 = severe

Differences in "n" reflects subject attrition, missed visits, or information not recorded.

2. Cornea Edema: Although the increase from baseline was significant in each group at each follow-up visit, the severity was not as marked as other signs of ocular inflammation. Also improvement was not as consistent, with no change in severity in either group between days 7 and 14. The therapeutic response was significantly different between investigators on Day 7, with Dr. Sabiston's subjects exhibiting significantly less severe corneal edema in the flurbiprofen group than in the vehicle group but no difference between groups was detected among Dr. Tessler's subjects (see sponsor's Table 6).

Table 6 - CORNEAL EDEMA

Day	Treatment	Severity* n	0	1	2	3	Mean Change From Baseline	SD	Within-Group p-value	Between-Group p-value
-3 (baseline)	FLUR	36	35	0	0	0	---	---	---	NS
	VEH	36	36	1	0	0	---	---	---	
3	FLUR	36	20	14	0	2	0.6	0.8	0.001	NS
	VEH	36	17	12	6	1	0.8	0.8	0.001	
7	FLUR	35	29	3	0	3	0.3	0.9	0.032	*
	VEH	35	23	10	2	0	0.4	0.6	0.001	
14	FLUR	34	26	6	0	1	0.3	0.6	0.015	NS
	VEH	34	23	[illegible]	2	0	0.4	0.6	0.002	

* 0 = none, 1 = mild, 2 = moderate, 3 = severe.

Differences in "n" reflect subject attrition, missed visits, or information not recorded.

* The results of the two investigators' populations were significantly different on Day 7, with significantly less severe corneal edema in the flurbiprofen group among Dr. Sabiston's subjects and no significant difference between groups among Dr. Tessler's subjects.

3. Anterior Chamber Cells: The difference in severity was not significant between the groups although it approached significance on day 14 with a p value of 0.058 (Sponsor's Table 7).

Table 7 - ANTERIOR CHAMBER CELLS

Day	Treatment	n	Severity* 0	1	2	3	Mean Change From Baseline	SD	Within-Group p-value	Between-Group p-value
-3 (baseline)	FLUR	36	36	0	0	0	---	---	---	NS
	VEH	36	36	0	0	0	---	---	---	
3	FLUR	36	9	12	15	0	1.2	0.8	0.001	
	VEH	36	9	10	10	7	1.4	1.1	0.001	NS
7	FLUR	35	15	14	5	0	0.7	0.7	0.001	
	VEH	35	12	13	9	1	1.0	0.9	0.001	NS
14	FLUR	34	19	13	1	0	0.5	0.6	0.001	
	VEH	34	14	12	8	0	0.8	0.8	0.001	NS(p=0.058)

* 0 = none, 1 = mild, 2 = moderate, 3 = severe.

Differences in "n" reflect subject attrition, missed visits, and information not recorded.

4. Anterior Chamber Flare: This was significantly less severe in the flurbiprofen treated group only on day 14 (sponsor's Table 8).

Table 8 - ANTERIOR CHAMBER FLARE

Day	Treatment	Severity* n	0	1	2	3	Mean Change From Baseline	SD	Within-Group p-value	Between-Group p-value
-3 (baseline)	FLUR	36	0	0	0	0	---	---	---	NS
	VEH	36	0	0	0	0	---	---	---	
3	FLUR	36	1	20	14	1	1.4	0.6	0.001	NS
	VEH	36	5	10	18	3	1.5	0.8	0.001	
7	FLUR	35	6	19	9	0	1.1	0.7	0.001	NS
	VEH	35	6	17	10	2	1.2	0.8	0.001	
14	FLUR	34	19	11	3	0	0.5	0.7	0.001	0.004
	VEH	34	9	14	10	1	1.1	0.8	0.001	

* 0 = none, 1 = mild, 2 = moderate, 3 = severe.

Differences in "n" reflect subject attrition, missed visits, or information not recorded.

Safety results: There were no reactions in either group that could be directly attributed to the study medications.

Summary: Two indicators of ocular inflammation, conjunctival injection and anterior chamber flare, were significantly less severe in the flurbiprofen group than in the vehicle group, but only on post-operative day 14. A third indicator, anterior chamber cells, was less severe in the flurbiprofen group approaching significance at p = 0.058, but again only at day 14. There were no significant between group differences for corneal edema.

B. Protocol No. FLUR-912-5827

Title: Summary and conclusion of a double-masked study to determine the anti-inflammatory effect of 0.03% flurbiprofen in intracapsular cataract extraction.

Investigator: Robert Stegmann, M.D.
Chief of Ophthalmology
Garankua Hospital
Pretoria, South Africa

Study Objective: To compare the effectiveness of 0.03% flurbiprofen to placebo in suppressing ocular inflammation as manifested following intracapsular cataract extraction.

Number of Subjects: Fifteen subjects (thirty eyes) with bilateral mature cataracts.

Study Design: Double masked with the first eye selected for surgery randomly assigned to 0.03% flurbiprofen or placebo. After unilateral cataract extraction, the assigned medication was instilled every four hours for one week. Then following a suitable interval determined by the investigator, the second eye underwent cataract extraction and post-operative treatment with the alternative medication (placebo or active drug) was instituted using the same schedule.

Safety Results: No adverse reactions were reported and no subjects were discontinued.

Efficacy Results: Conjunctival injection, anterior chamber flare and anterior chamber cells were evaluated on day -3, 3, 7 and 14 (the study protocol only called for 7 days of observation but was extended to 14 by the investigator) according to a subjective scale of none(0), mild(1), moderate(2) and severe(3). Significantly less reaction occurred in flurbiprofen treated subject for the following parameters on the days indicated (Mann-Whitney P-value):

Day 3

1. Anterior chamber flare ($p = 0.0251$)
2. Conjunctival injection ($p = 0.0310$)

Day 7

1. Anterior chamber cells ($p = 0.0550$)
2. Conjunctival injection ($p = 0.0161$)

Day 14

No between group differences

C. Protocol No. FLUR-909-5827

Title: A double-masked controlled comparison of 0.03% flurbiprofen to placebo in treatment of bilateral intracapsular cataract extraction-induced ocular inflammation.

Investigator: Robert Stegmann, M.D.
Chief of Ophthalmology
Garankua Hospital
Pretoria, South Africa

Number of Subjects: 15 (scheduled for bilateral cataract surgery).

Study Objective and Design: Identical to FLUR-912-5827 except patient evaluations were carried out on day 2, 4 and 7.

Safety Results: No adverse effects reported and no patients were discontinued.

Efficacy Results: A clinical score of 0 to 4+ was used to grade the degree of conjunctival injection, anterior chamber flare, and anterior chamber cells on days 2, 4 and 7 for each eye. A statistically significant difference ($p < 0.05$) favoring flurbiprofen treatment was found for all three parameters at all three grading times.

D. Protocol No. FLUR-114-5827

Title: Efficacy and safety of Flurbiprofen in minimizing the severity of ocular inflammation after intracapsular extraction.

Investigator: Robert Stegmann, M.D.
Pretoria, South Africa

Number of Subjects: 19

Study Design: Two week, randomized double-masked, parallel-group, placebo controlled study.

Results: There were no significant differences in severity of signs of inflammation between the two groups during the study. There were no adverse reactions.

E. Protocol No. FLUR-106-5827

Title: Efficacy and Safety of Sodium Flurbiprofen Ophthalmic Solution (alone and in combination with dexamethasone) in preventing ocular inflammation following cataract extraction and intraocular lens implantation.

Investigator: Michael Blumenthal, M.D.
Chairn Seba Medical Center
Sackler School of Medicine
Tel-Hashower, Israel

Study Design: Six-week, parallel-group, double-masked, randomized clinical trial. Subjects were assigned to be treated with either 0.03% flurbiprofen or its vehicle, with 0.17% dexamethasone added to the regimen if the investigator felt that an additional anti-inflammatory agent was necessary. Consequently there were four treatment groups: flurbiprofen, flurbiprofen/dexamethasone, vehicle/dexamethasone and vehicle.

Number of Subjects: Forty-four subjects (45 eyes) were entered into the study, and data from 43 subjects (43 eyes) were analyzed. (Data for subjects 42 and 43 were not supplied by the investigator.)

Results

A. Safety: No subjects were terminated from the study for reasons related to study medications. Seven subjects developed post-operative hyphema during the course of the study; two (subjects 13 and 16) were severe. Both of these were in the flurbiprofen/dexamethasone group, as were three other hyphema cases. One subject with hyphema was in the flurbiprofen only group and one was in the vehicle only group.

B. Efficacy: No significant difference in the speed of disappearance of post-operative inflammation could be detected between the flurbiprofen treated and vehicle only treated groups. The investigator elected to add dexamethasone to 14 of 23 subjects (61%)

treated with vehicle and 10 of 20 subjects (50%) treated with flurbiprofen.

II. Control of Ocular Inflammation after Argon Laser Trabeculoplasty

A. Protocol No. FLUR-109/117-5827

Title: Flurbiprofen - Effect of Topical Flurbiprofen on Outcome of Argon Laser Trabeculoplasty for Primary Open Angle Glaucoma.

Investigators: Alan Robin, M.D.
Harry Quiglely, M.D.
Michael Blumenthal, M.D.
George Baerveldt, M.D.
Jacob Wilensky, M.D.
Robert Weinreb, M.D.
E. George Rosanelli, M.D.

Objective and Study Design: This was a five week, parallel group double-masked clinical study to evaluate the anti-inflammatory activity, IOP-lowering potential, and safety of 0.03% flurbiprofen ophthalmic solution after argon laser trabeculoplasty (ALT).

Subjects received either 0.03% flurbiprofen ophthalmic solution or flurbiprofen vehicle, the study regimen was initiated with a six-drop loading dose: one drop every 20 minutes into the study eye beginning two hours before ALT. Post ALT, one drop was instilled every four waking hours for seven consecutive days.

Number of Subjects: 68 in the flurbiprofen group, 62 in the vehicle group.

Results

Safety: Both the vehicle and active drug were well tolerated, however, there was a significantly greater number of reports of blurring of vision for subjects in the flurbiprofen group compared with the vehicle group. Three other adverse events occurred which the investigators felt were possibly drug related, two in the flurbiprofen group and one in the vehicle group.

Efficacy: There was a significant difference ($p < 0.05$) in the data favoring the flurbiprofen treatment group for conjunctival injection, the maximum inflammation score, and the investigator's assessment of treatment. However, this beneficial effect was not accompanied by a parallel reduction in mean peak intraocular pressure rise after the surgery.

B. Protocol No. FLUR-110-5827

Title: Efficacy and safety of 0.03% Flurbiprofen Ophthalmic Solution on the Outcome of Argon Laser Trabeculoplasty Among Subjects with Secondary Glaucoma.

Investigators: Alan Robin, M.D.
Michael Blumenthal, M.D.
George Baerveldt, M.D.
Jacob Wilensky, M.D.
Robert Ritch, M.D.

Objective and Study Design: Identical to FLUR 109/117-5827 except the subjects had various forms of secondary glaucoma.

Number of Subjects: 80 eyes (80 subjects); 42 were in the flurbiprofen groups and 38 were in the vehicle group.

Results

Safety: No subjects in either group were terminated for treatment-related reasons. There were significantly more reports of burning in the flurbiprofen group, and significantly more reports of tearing in the vehicle group.

Efficacy: Both groups exhibited a significant increase in inflammation during the first 24 hours after ALT. Significantly less ($p < 0.05$) inflammatory reaction occurred for several parameters in the flurbiprofen treated group at the times indicated:

1. Conjunctival Injection: Hour 3 and Day 1
2. Anterior Chamber Cells: Day 1
3. Anterior Chamber Flare: Day 1 and Day 7
4. Corneal Edema: No differences

At day seven there were no difference except for anterior chamber flare.

Intraocular pressure responses and ultimate clinical success of the ALT were not different in the flurbiprofen and vehicle groups.

Five weeks after surgery, signs of inflammation had returned to baseline in all but six subjects, who were considered by the investigator to have uncontrolled intraocular inflammation. Only one of these subjects was in the flurbiprofen group.

III. Control of Ocular Inflammation after Miscellaneous Ocular Surgery

A. Protocol FLUR-918-5287

Title: To Determine the Anti-Inflammatory Effect of Flurbiprofen versus that of Dexamethasone and Placebo in Cyclocryotherpay.

Investigator: George Ipaeth, M.D.
Philadelphia, PA 19118

Number of Subjects: 42

Study Design: Six week, randomized, double-masked study. Conjunctival erythema, anterior chamber flare and cells, and intraocular pressure were evaluated on Days 0, 2, 3, 7, and 14.

Safety Results: No adverse reactions occurred and no subjects were discontinued from the study.

Efficacy Results:

1. Anterior Chamber Flare: Between group comparison revealed no statistically significant differences.

2. Anterior Chamber Cells: No statistically significant differences between the flurbiprofen and the placebo groups were observed on any study day.

3. Conjunctival Erythema: No statistically significant difference between the flurbiprofen group and the placebo group was observed except on Day 14 when erythema was worse in the flurbiprofen group.

Summary: Flurbiprofen was found to be no better than placebo in the treatment of inflammation induced by cyclocryotherapy.

B. Protocol FLUR 105-5827: This study was designed to evaluate the efficacy of preventing post-vitrectomy rubeosis and iritis among diabetic subjects. No conclusions regarding efficacy could be drawn from the results of this study due to poor enrollment. However, five subjects in the study received flurbiprofen for up to three months without adverse effects.

IV. Inhibition of Miosis Induced During Cataract Surgery

A. Protocol FLUR 107-5827

Title: The Efficacy and Safety of Sodium Flurbioprfen Compared with Vehicle in the inhibition of Surgically Induced Miosis.

Investigator: Richard H. Keates, M.D.
456 Clinic Drive
Columbus, OH 43210

Study Design: Double-masked clinical study with 34 subjects randomly assigned to the flurbiprofen or vehicle treatment groups. At hours 3, 2, 1, and at 45 and 30 minutes before surgery, all subjects received a single drop of masked treatment into the eye scheduled for surgery.

Three measurements of pupil diameter were made: 1) just before surgery, 2) after irrigation and aspiration of the lens material, and 3) after administration of miochol.

Results: Pupil diameters and changes in pupil diameter were compared between groups using one-way analysis of variance. The change in pupil diameter within each group was tested for significance using a paired t-test. A p-value less than or equal to .05 was considered statistically significant.

Pupil Diameter: A significant pupillary constriction from baseline occurred in both treatment groups after lens irrigation and aspiration, but the mean change was significantly less in the flurbiprofen group (29.9%) than in the vehicle group (45.6%).

Miochol was administered to 13 subjects in the flurbiprofen group and 10 subjects in the vehicle group, decreasing pupil diameter significantly within each group, but without a significant difference between the two groups.

There were no adverse effects noted during the study.

B. Protocol FLUR 111-5827

Study Objectives

1. To compare the efficacy and safety of 0.03% Flurbiprofen with its vehicle when given preoperatively to inhibit the miosis induced during the course of cataract surgery.

2. To evaluate the effect of 0.03% Flurbiprofen on the miotic effect of Miochol.

Investigators: Thomas H. Pettit, M.D.
Bradley R. Straatsma, M.D.
Jules Stein Eye Institute
UCLA School of Medicine
Los Angeles, CA 90024

Number of Subjects: 48

Study Design: Double-masked, parallel group study performed during cataract surgery with random assignment of subjects to the flurbiprotein or vehicle treatment groups. Each subject was treated preoperatively with a total of four drops.

Results: The mean percent decreases from baseline in pupil diameter and area were significantly less in the flurbiprofen group than in the vehicle group for Dr. Pettit's patients ($p = 0.03$) but not for Dr. Straatsma's patients ($p = 0.26$).

The mean percentage decreases from baseline in pupil diameter were as follows:

	Dr. Straatsma	Dr. Pettit
Flurbiprofen group	39%	38%
Vehicle group	38%	52%

Inspection shows a significant difference between the vehicle groups for the two doctors. The surgeons agreed that their operative techniques were different, and that Dr. Pettit performed cataract surgery less frequently than Dr. Straatsma. This implies that Dr. Pettit's patients incurred more iris trauma during their surgery accounting for the greater miosis in his control group. This finding is consistent with the hypothesis that excessive miosis during cataract surgery is caused by prostaglandins released by the iris during trauma and that pretreatment with a drug capable of inhibiting prostaglandin production acts to inhibit miosis by preventing trauma-induced prostaglandin release.

[illegible] administered to 22 subjects in the flurbioprfen group and 22 [illegible] vehicle group (pooled data). The mean pupil diameter [illegible] flurbiprofen group and 28% in the vehicle group.

[illegible] were noted in either study group.

V. Safety and Comfort Studies

A. Protocol FLUR 910-5827: The conclusion was reached that 0.03% flurbiprofen produced mild or moderate stinging upon ocular instillation that was acceptable clinically. Flurbiprofen 0.1% produced excessive stinging and burning and therefore the 0.03% solution was utilized in all additional studies.

B. Protocol FLUR 911-5827: Eleven volunteers received one drop of 0.03% flurbiprofen in one eye and one drop of vehicle to the other eye four times daily for 3 days in a double-masked study. Burning and stinging were noted on 90% of the instillations of flurbiprofen, but in only 6.7% of the placebo installations. No eyes were discontinued due to ocular intolerance and no volunteers dropped out of the study because of the burning or stinging from flurbiprofen.

C. Protocol FLUR 920-5827

Title: One Month Safety Study of the Ocular and Systemic Effects of 0.03% Flurbiprofen.

Investigator: Irving Leopold, M.D., D. Sci, (Med)
Irvine Eye Institute
19732 MacArthur Boulevard
Irvine, CA 92713

Study Design: Twenty-three normal, healthy and ocularly asymptomatic volunteers received one drop of open-labeled 0.03% flurbiprofen in both eyes four times daily for one month.

Results:

Safety:

1. Ten of the 23 participants reported burning and stinging with flurbiprofen.
2. One participant showed a 2-line decrease in vision at one visit only.
3. One participant voluntarily discontinued usage at day 26 due to an enlarged vessel in the left eye and headaches.
4. Heart rate decreased by 3.3 to 3.9 beats per minute, but there were no changes in blood pressure or respiration rate parameters.
5. There was a significant decrease in intraocular pressure on days 5 and 30.
6. A significant increase in pupil size occurred on days 15 and 30.

Efficacy results: not applicable.

VI. Intraocular Pressure Studies

A. Protocol FLUR 916-5827

Title: Double-masked comparison of Flurbiprofen to Dexamethasone of the Intraocular Pressure of Volunteers Known to be Pressure Responsive to Corticosteroid Treatment.

Investigator: Michael Kass, M.D.
Washington University Medical School
Department of Ophthalmology
St. Louis, MO 63110

Study Design: Ten volunteers, ocularly asymptomatic, who had been identified in previous studies to be pressure responsive to a predictable degree to the topical use of dexamethasone eyedrops, were admitted to this study. The masked medication units were randomized so that one eye received 0.03% flurbiprofen and the fellow eye received 0.1% dexamethasone phosphate. Dosage of each medication was one drop four times daily during the waking hours.

Results

Safety: The flurbiprofen treated eyes of all ten volunteers experienced mild to moderate stinging and burning.

Efficacy: The IOP of flurbiprofen treated eyes did not change significantly for any eye throughout the 6 week study. The dexamethasone treated eyes showed a significant increase in IOP from baseline to Week 6 of 13.10 mm Hg. Additionally there were four dexamethasone treated eyes that exhibited marked pressure elevations equal to or greater than 32 mm Hg at Week 3 and were subsequently terminated from the study. The fellow eyes of these 4 patients (treated with flurbiprofen) continued in the study for six weeks without sustaining elevated intraocular pressure.

B. Protocol FLUR 917-5827

Title: Double-masked Study of the Interactive Effect of Flurbiprofen used Concomitantly with Dexamethasone on the Intraocular Pressure of Volunteers Known to be Pressure Responsive to Corticosteroid Treatment.

Investigator: Michael Kass, M.D.
St. Louis, MO 63110

Study Design: Ten volunteers, previously identified as pressure responders, underwent one week of pretreatment of one eye with masked flurbiprofen, while the fellow eye received vehicle only. At the end of the one week pretreatment interval, open labeled 0.1% dexamethasone phosphate was added to the dosage regimen, for both eyes, 15 minutes after the administration of the masked flurbiprofen and placebo for 6 weeks.

Results

Safety: Four patients were discontinued at Week 3 due to increased intraocular pressure above or equal to 32 mm Hg.

No patients were discontinued due to adverse effects of flurbiprofen.

Efficacy: Tonography results showed a significant and equal decrease in outflow from baseline in both treated eyes.

Conclusion: Flurbiprofen, while safe and well tolerated at the 0.03% concentration did not control the response of intraocular pressure in individuals known to be pressure responsive to corticosteroid therapy.

VII. Control of Inflammation in Various Ocular Structures.

1. External Inflammation: The conditions studied included non-infectious and vernal conjunctivitis, episcleritis, superior limbic keratitis, Thygesonic's superficial punctate keratitis, corneal melting syndrome and histamine-antigen induced conjunctivitis. In the vernal conjunctivitis study there was no difference in ocular inflammation between flurbiprofen and vehicle-treated subjects. No conclusions could be drawn form the results of the remaining studies because of poor enrollment.

2. Anterior Segment Inflammation: The conditions studied included uveitis iritis and cyclitis. 0.03% flurbiprofen appeared to be as efficacious as dexamethasone in the treatment of anterior uveitis, but no conclusion could be drawn from compassionate case studies of the other conditions. Flurbiprofen appeared to be safe for periods up to 3 months.

3. Posterior Pole Inflammation: Three studies (one clinical and two compassionate cases) made an attempt to evaluate the efficacy of 0.03% flurbiprofen in the prevention and treatment of cystoid macular edema. Useful data concerning efficacy was not obtained, but flurbiprofen treatment up to two years was not associated with adverse effects.

Summary Statements

1. Flurbiprofen interferes with prostaglandin synthesis through inhibition of the enzyme cyclo-oxygenase.

2. Flurbiprofen was demonstrated in animal models to be a potent inhibitor of induced inflammation and of corneal neovascularization. The latter may be correlated with significantly lower corneal wound strengths that have been demonstrated in flurbiprofen treated rabbit corneas.

3. Flurbiprofen has no carcinogenic potential in the mouse.

4. Flurbiprofen at dosage levels from 0.675 to 25 mg/kg daily in Boots-Wistar rats caused a prolongation of pregnancy with uterine hemorrhage, an increase in stillbirths and reduction in litter survival.

5. The ingestion of a single table of flurbiprofen has apparently caused a near-fatal attack of bronchospasm in patient with asthma.

6. Study FLUR 130/919-5827 comparing flurbiprofen to vehicle after intracapsular cataract extraction demonstrated superiority of the test drug for conjunctival injection and anterior chamber flare at day 14 only. Anterior chamber cells and corneal edema were unaffected by the therapy.

7. Two studies carried out by Robert Stegmann, M.D. of Pretoria, South Africa studied a total of 30 patients (15 in each study) undergoing bilateral intracapsular cataract extraction (60 eyes). The first eye selected for surgery was randomly assigned to 0.03% flurbiprofen or placebo and the second eye received the alternative medication. The first study (FLUR 912-5827) showed a significant advantage for flurbiprofen on post-operative day 3 for anterior chamber flare and conjunctival injection and on day 7 for anterior chamber cells and conjunctival injection. The second study (FLUR-909-5827) demonstrated superiority of flurbiprofen over vehicle for conjunctival injection, anterior chamber flare and anterior chamber cells on post-operative day 2, 4 and 7.

8. A third study by Dr. Stegmann of similar design to the two studies summarized under point 7 above, utilizing 19 patients failed to demonstrate superiority for flurbiprofen over vehicle, in the control of ocular inflammation following intracapsular cataract extraction.

9. Study FLUR-106-5827 investigated flurbiprofen alone and in combination with dexamethasone in preventing ocular inflammation following cataract extraction and intraocular lens implantation. Seven eyes (total 45) developed hyphema (two severe). Five of these including the two severe cases were in the flurbiprofen/dexamethasone group. The type of lenses used (iris clip) which probably made these eyes more susceptible to the anti-clotting properties of these drugs, are no longer in use today. Superiority for flurbiprofen over vehicle in controlling post-operative inflammation was not demonstrated. The investigators elected to add dexamethasone to 61% of subjects treated with vehicle only and to 50% of subjects treated with flurbiprofen only.

10. Two studies FLUR 109-5827 and 110-5827 addressed the safety and efficacy of flurbiprofen in the treatment of inflammation from Argon Laser Trabeculoplasty. Both studies demonstrated significant efficacy for the flurbiprofen versus vehicle in reducing the inflammatory response. However, these beneficial effects were not accompanied by a parallel reduction in mean peak intraocular pressure rise after surgery, nor was the ultimate clinical success of the procedure different in the flurbiprofen and vehicle groups.

11. Flurbiprofen was not better than placebo in the treatment of inflammation induced by cyclocryotherapy. It should be noted that this is a very severe form of inflammation that also does not respond well to steroid therapy.

12. Two studies (FLUR 107-5827 and 111-5827) demonstrated flurbiprofen to be more effective than placebo in preventing miosis during cataract surgery, except for Dr. Straatsma's group (111-5827) where this was not true. Dr. Straatsma is a highly skilled surgeon and it is presumed that less prostaglandin release from iris trauma occurred in his patients. [illegible] not prevent Miochol induced miosis.

[illegible] 27) does not elevate intraocular pressure in [illegible] this response to topical steroids.

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8. A third study by Dr. Stegmann of similar design to the two studies summarized under point 7 above, utilizing 19 patients failed to demonstrate superiority for flurbiprofen over vehicle, in the control of ocular inflammation following intracapsular cataract extraction.

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11. Flurbiprofen was not better than placebo in the treatment of inflammation induced by cyclocryotherapy. It should be noted that this is a very severe form of inflammation that also does not respond well to steroid therapy.

12. Two studies (FLUR 107-5827 and 111-5827) demonstrated flurbiprofen to be more effective than placebo in preventing miosis during cataract surgery, except for Dr. Straatsma's group (111-5827) where this was not true. Dr. Straatsma is a highly skilled surgeon and it is presumed that less prostaglandin release from iris trauma occurred in his patients. Flurbiprofen did not prevent Miochol induced miosis.

13. Flurbiprofen (FLUR 916-5827) does not elevate intraocular pressure in subjects known to demonstrate this response to topical steroids.

14. The potential efficacy of flurbiprofen in the treatment of external ocular inflammations, anterior segment inflammation and cystoid macular edema was evaluated in several studies, but no conclusions could be drawn due to inadequate enrollment of subjects. Some subjects received flurbiprofen up to two years without apparent adverse effects.

15. The major adverse effect of flurbiprofen from topical administration to the eye is burning and stinging which occurs in up to 90% of subjects. Transient blurring of vision and increased bleeding tendency of iris were reported infrequently and were not clearly related to the drug.

Overall Evaluation and Conclusions: Flurbiprofen is a nonsteroid anti-inflammatory product studied in this NDA in a 0.03% solution for topical ophthalmic use. It is one of a series of phenylalkanoic acids with a mechanism of action believed to be mediated through inhibition of the cyclo-oxygenase enzyme that is essential in the biosynthesis of prostaglandins. The sponsor has proposed its use for the treatment of post-cataract extraction and postlaser trabeculoplasty inflammation and also for the inhibition of intraoperative miosis.

The efficacy of flurbiprofen in the treatment of inflammation induced by cataract extraction was weakly supported by study 130/919-5827 which showed it to be effective only on the 14th post-operative day and only for conjunctival injection and anterior chamber flare; anterior chamber cells and corneal edema were unaffected.

Two studies by a single investigator (912-5827 and 909-5827) comprising 30 patients demonstrated superiority of flurbiprofen over vehicle in the control of conjunctival injection and anterior chamber cell and flare during the first post-operative week. An additional study of 19 patients by the same investigator failed to show any advantage for flurbiprofen over vehicle in the control of inflammation induced by cataract extraction.

Another study (106-5827) in 45 eyes that underwent cataract extraction with intraocular lens inplantation failed to show efficacy for flurbiprofen in the control of post-operative inflammation.

Two double masked studies by the same investigator group, one in primary glaucomas and the other in secondary glaucomas demonstrated efficacy for flurbiprofen in the control of anterior segment inflammation induced by argon laser trabeculoplasty. However, this reduction in inflammation did not ameliorate the post-operative elevation of pressure that occurs in some patients during the first 24 hours, nor did it effect the final therapeutic outcome of the procedure.

Flurbiprofen has been clearly demonstrated not to raise intraocular pressure when administered to subjects known to have an adverse pressure response to topical steroids.

Two adequate and well controlled controlled studies demonstrated that flurbiprofen is efficacious n the prevention of miosis during cataract surgery without interfering with acetylcholine induced miosis.

C. Control of miosis during cataract surgery.

1. Study FLUR 107-5827 - supported efficacy of flurbiprofen.

2. Study FLUR 111-5827 - Two separate investigators cooperated in this study, but efficacy for flurbiprofen was demonstrated for only one of them.

Labeling Review: The labeling is satisfactory except the word "postoperative" should be deleted from the Indications and Usage section.

Recommendations: Flurbiprofen is recommended for approval for the control of inflammation after argon laser trabeculoplasty and for the prevention of miosis during cataract surgery. Approval is not recommended for control of inflammation after cataract surgery.

David G. Harper MD
David G. Harper, M.D.

cc:
Orig NDA
HFN-340
HFN-815
HFN-815/CSO
HFN-815/DGHarper:bam:6/27/85
0594S

HFN-815 for E.T. 5 Aug 85

C. Control of miosis during cataract surgery.

1. Study FLUR 107-5827 - supported efficacy of flurbiprofen.

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Labeling Review: The labeling is satisfactory except the word "postoperative" should be deleted from the Indications and Usage section.

Recommendations: Flurbiprofen is recommended for approval for the control of inflammation after argon laser trabeculoplasty and for the prevention of miosis during cataract surgery. Approval is not recommended for control of inflammation after cataract surgery.

David G. Harper MD
David G. Harper, M.D.

cc:
Orig NDA
HFN-340
HFN-815
HFN-815/CSO
HFN-815/DGHarper:bam:6/27/85
0594S

DHCD for E.T. 5 Aug 85

Medical Officer's Addendum of NDA 19-404

Date: September 9, 1986

Sponsor: Allergan Pharmaceuticals

Name of Drug: Flurbiprofen Ophthalmic Solution

Purpose of Addendum: Response to Division Director's memorandum of July 11, 1986, requesting additional information for several studies.

I. Control of Ocular Inflammation after Argon Laser Trabeculoplasty.

Two studies, Protocol Nos. FLUR-109/117-5827 and FLUR-110-5827, addressed this issue. In the original MOR, based on significant differences in certain aspects of the inflammatory response post laser trabeculoplasty, Flurbiprofen Ophthalmic Solution was recommended for approval for this problem. On further review of these studies it was noted that they are not separate independent studies, nor do they address the same type of patients. Four investigators are common to both studies and FLUR-109/117-5827 studied primary chronic open angle glaucoma whereas FLUR-110-5827 studied patients with various secondary glaucomas.

Based on this re-evaluation of the studies, the recommendation that Flurbiprofen Ophthalmic Solution be approved for the treatment of inflammation in glaucoma patients undergoing Argon Laser Trabeculoplasty is withdrawn.

II. Inhibition of Miosis During Cataract Surgery: additional data was requested for the studies supporting this indication.

Study FLUR-107-5817 (Richard H. Keates, M.D.): The percent decrease from baseline in the pupil size was 45.6% for the vehicle and 29.9% for Flurbiprofen. This percentage is derived from a mean decrease in pupil size from baseline of 3.9 mm for the vehicle and 2.5 mm for Flurbiprofen (a 1.4 mm mean difference in pupil diameter before and after irrigation and aspiration of the lens). This is statistically significant ($p = 0.003$) as can be seen in Sponsor's Table 9.

TABLE 9

Pupil Diameter (mm): Before and After Irrigation and Aspiration of the Lens

	Treatment	n	Mean	SD	Range	Within-group p-value	Between-group p-value
Baseline (Pre-conjunctival Incision)	Flurbiprofen	16	8.3	1.1	5.0 to 9.0	—	
	Vehicle	18	8.4	0.6	7.0 to 9.3	—	NS
Post-Irrigation & Aspiration	Flurbiprofen	16	5.8	1.2	3.5 to 8.0	—	—
	Vehicle	18	4.6	1.3	2.0 to 6.3	—	
Change from Baseline	Flurbiprofen	16	-2.5	1.2	-5.0 to -0.5	< 0.001	0.003
	Vehicle	18	-3.9	1.3	-7.0 to -2.0	< 0.001	
% Decrease from Baseline	Flurbiprofen	16	29.9	12.7	7.1 to 55.6	< 0.001	0.003
	Vehicle	18	45.6	14.9	28.6 to 77.8	< 0.001	

Study FLUR 111-5827 (Thomas H. Pettit, M.D. and Bradley R. Straatsma, M.D.: Pupil diameter measurements before and after nucleus expression showed significantly less pupil constriction ($p = 0.03$) in the Flurbiprofen treated group versus the vehicle treated group for investigator Pettit (See abstract of Sponsor's Table 11):

Table 11

HORIZONTAL PUPIL DIAMETER (mm): BEFORE AND AFTER NUCLEUS EXPRESSION

Investigator Pettit

	Flurbiprofen			Vehicle			
	n	Mean	S.D.	n	Mean	S.D.	p-value
Baseline	11	8.57	0.87	14	8.24	0.80	
Post-nucleus expression	11	-1.84	0.72	14	-2.49	1.07	
% Change		-21%	10		-30%	12	0.03

Investigator Straatsma did not show a statistically significant difference in pupil size before and after nucleus expression between Flurbiprofen and vehicle treated groups (See abstract of Sponsor's Table 12).

Table 12

HORIZONTAL PUPIL DIAMETER (mm): BEFORE AND AFTER NUCLEUS EXPRESSION

Investigator Straatsma

	Flurbiprofen			Vehicle			
	n	Mean	S.D.	n	Mean	S.D.	p-value
Baseline	12	8.00	0.59	11	8.24	0.87	
Post-nucleus expression	12	-1.71	0.73	11	-1.50	0.95	
% Change		-21%	9		-18%	11	0.26

Study FLUR 111-5827 (Thomas H. Pettit, M.D. and Bradley R. Straatsma, M.D.: Pupil diameter measurements before and after nucleus expression showed significantly less pupil constriction ($p = 0.03$) in the Flurbiprofen treated group versus the vehicle treated group for investigator Pettit (See abstract of Sponsor's Table 11):

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Baseline	11	8.57	0.87	14	8.24	0.80	
Post-nucleus expression	11	-1.84	0.72	14	-2.49	1.07	
% Change		-21%	10		-30%	12	0.03

Investigator Straatsma did not show a statistically significant difference in pupil size before and after nucleus expression between Flurbiprofen and vehicle treated groups (See abstract of Sponsor's Table 12).

Table 12

HORIZONTAL PUPIL DIAMETER (mm): BEFORE AND AFTER NUCLEUS EXPRESSION

Investigator Straatsma

	Flurbiprofen			Vehicle			
	n	Mean	S.D.	n	Mean	S.D.	p-value
Baseline	12	8.00	0.59	11	8.24	0.87	
Post-nucleus expression	12	-1.71	0.73	11	-1.50	0.95	
% Change		-21%	9		-18%	11	0.26

The two studies in support of this indication (inhibition of miosis during cataract surgery) are geographically independent and three of the total of four investigators had statistically significant results independently of one another and without a need to pool the data. Therefore, the original MOR recommendation to approve Flurbiprofen for this indication is retained.

Flurbiprofen and Intraocular Pressure: The results of two studies FLUR 916-5827 and FLUR 917-5827 show that Flurbiprofen does not influence intraocular pressure in steroid sensitive individuals. That is, it neither causes a rise in IOP in individuals known to experience a rise from topically administered steroids, nor does it protect against such a rise in these individuals when they are challenged with steroids after pretreatment with Flurbiprofen.

Recommendations: Flurbiprofen is recommended for the prevention of miosis during cataract surgery as in the original MOR. The previously made recommendation for approval for the control of inflammation after argon laser trabeculoplasty is rescinded on the basis that there were not two geographically independent studies for this indication.

David G. Harper, M.D.

cc:
Orig NDA
HFN-815
HFN-815/CSO/RLinkous
HFN-340
HFN-815/DGHarper:js/9/9/86
1480m

CHEM REVIEW

Division of Anti-Infective
Drug Products
Chemist's Review #1
Date Completed: 4/4/85

A.1. NDA 19-404

Sponsor: Allergan Pharmaceuticals, Inc.
Irvine, CA 92715

2. Product Names:

Non-proprietary: flurbiprofen ophthalmic solution
USAN: flurbiprofen is the free acid.

3. Dosage Form & Route of Administration: Solution, topical

4. Pharmacological Category and/or Principal Indication: For treatment of postoperative and postlaser trabeculoplasty inflammation of the anterior segment of the eye. Also, for the treatment of intraoperative miosis.

C. Remarks:
This product is classified as 1-B.

W. F. Kochert
William F. Kochert

cc: Orig. NDA
~~HFN-815~~ HFN-815/CSO HFN-815/Kochert: gm 4/6/85
~~R/D Init. by:~~ ARCasola 4/8/85 ARC 4/8/85
HFN-815/MO
3631b

Chemist Review Notes:

1. Components: All components are listed.

3. Facilities: Allergan Pharmaceuticals, Inc.
Irvine, CA 92713

Allergan, Inc.
Point Claire
Quebec
Canada

Allergan Pharmaceuticals Ireland, Ltd.
Westport
County Mayo
Ireland

Allergan America and Allergan Carribean
Hormiqueros, Puerto Rico

Facilities are described in detail
satisfactory.

4. Personnel:
The qualification and experience of the key personnel at each facility are given in and are satisfactory.

Division of Anti-Infective
Drug Products
Chemist's Review #2
Date Completed: 1/14/86

A.1. NDA 19-404

Sponsor: Allergan Pharmaceuticals, Inc.
Irvine, CA 92715

2. Product Names:

Non-proprietary: flurbiprofen ophthalmic solution
USAN: flurbiprofen is the free acid.

3. Dosage Form & Route of Administration: Solution, eye drops

4. Pharmacological Category and/or Principal Indication: For treatment of postoperative and postlaser trabeculoplasty inflammation of the anterior segment of the eye. Also, for the treatment of intraoperative miosis.

5. Structural Formula and Chemical Name(s):

B. 1. Amendments: Aug. 2, 1985

Ireland and Allergan, Canada.
NDA is not approvable. (Plant inspections not received).

William F. Kochert

cc: Orig. NDA
HFN-815 HFN-815/CSO HFN-815/Kochert:gm 1/16/86
HFN-815/MO R/D initialed by: ARCasola 1/15/86 ARC 1/22/86
0194c

Labeling:

The draft bottle label, carton and insert are satisfactory.

Division of Anti-Infective
Drug Products
Chemist's Review #3
Date Completed: 3/5/86

A.1. NDA 19-404

Sponsor: Allergan Pharmaceuticals, Inc.
Irvine, CA 92715

2. Product Names:

Non-proprietary: flurbiprofen ophthalmic solution
USAN: flurbiprofen is the free acid.

3. Dosage Form & Route of Administration: Solution, topical

4. Pharmacological Category and/or Principal Indication: For treatment of postoperative and postlaser trabeculoplasty inflammation of the anterior segment of the eye. Also, for the treatment of intraoperative miosis.

5. Structural Formula and Chemical Name(s):

B. 1. Initial Review: -

C. Remarks:
Chemist's review dated 1/14/86 stated that NDA is not approvable in the absence of plant inspections evaluation.
Memo dated 2/28/86 from Compliance (HFN-322) stated that
were in compliance with GMPs.

D. Conclusions and/or Recommendations:
NDA is now approvable from the standpoint of manufacturing controls.

W.F. Kochert
William F. Kochert

cc: Orig. NDA
HFN-815
HFN-815/MO
0239c

HFN-815/CSO
R/D initialed by: ARCasola 3/6/86

HFN-815/Kochert:gm 3/7/86
ARC 3/10/86

PHARM
REVIEW

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-404 (Amendment [redacted]

Date Review Completed: 3/5/85

Applicant: Allergan Pharmaceuticals, Inc., Irvine, CA

Drug: Flurbiprofen Ophthalmic Solution (0.03%)

Category: Nonsteroidal anti-inflammatory

Indication: For treatment of postoperative & post-laser trabeculoplasty inflammation and for the inhibition of intraoperative miosis

Related Submission: [redacted]

Preclinical Studies: No new studies have been submitted.

Comments: In a previously provided one-year topical ocular toxicity study in rabbits, "status spongiosis" described as "clear, round empty vacuoles within optic nerve neural substance" or "scattered throughout neuropil of the central nervous system" were reported. At interim sacrifice (3 mos.), the incidence was found to be dose-related for the brain. I had, therefore, recommended that the sponsor perform another 90-day ocular study with an untreated control group and a high-dose group, to determine if the observed "status spongiosis" was actually an artefact, as has been claimed by the applicant (Pharm. Rev. dated 11/7/84). Later during a telephone conversation with Mr. Bostwick, the applicant stated that subsequent examination of brains & optic nerves from some normal untreated rabbits also had similar findings. These results have been submitted now for our review. In 9/12 animals, the lesions were present in the brain. In 6 animals where "the plane of section allows evaluation of the optic nerve head" also similar lesions were observed. Thus, it appears that the lesions are either artefactual (perhaps formed during fixation) or are normally present in the colony of rabbits used in these experiments. Although artifactual origin of such lesions is a distinct possibility, the fact remains that at interim sacrifice (see above), there was a clear dose-related increase in incidence in the treated groups, whereas it remained constant in the various brain areas (20% incidence) in the vehicle control gp. The other problem in comparing the results is that the untreated animals examined later appear to be not of the same age and weights (smaller brain) according to the pathologists.

Recommendations:

1. The applicant should perform a 90-day toxicity study as recommended earlier ((IND) Pharm. Rev. dated 11/7/84). Only microscopic exam of the optic nerve head and the CNS would be sufficient.

2. The one year study submitted earlier and the pathologist's report submitted in this amendment appear to have been completed in late 1979 and early 1980, respectively. The applicant should explain why these reports were not submitted earlier during the clinical investigation phase.

Syed M. Alam, Ph.D.

cc: Orig. NDA
HFN-815 ST 4/12/85
HFN-815/MO
CSO
HFN-340
HFN-815/SNAlam/smc/3/14/85
R/d init.by:JMDavitt
3415b

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-404 (Original Submission, dated 12/19/84)

Date Review Completed: 5/14/85

Applicant: Allergan Pharmaceuticals, Inc., Irvine, CA

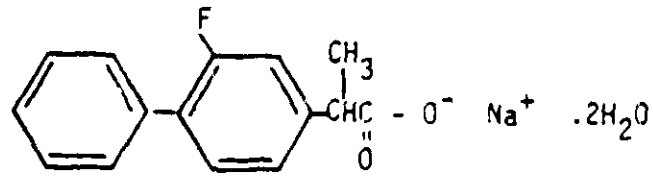
Drug: Flurbiprofen (FBP) Ophthalmic Solution (0.03%)

Generic Name: Sodium flurbiprofen

Code Designation: GSH-1334 (Allergan); BTS-18,322 (Boots); U-28,182 (Upjohn)

Chemical Name: 2-(2-fluoro-4-biphenyl) propionic acid, sodium, dihydrate

Chemical Structure:



Composition:

Ingredient	Percent (w/v)

Category: Non-steroidal anti-inflammatory drug (NSAID)

Clinical Indication: Treatment of post-operative & post-laser trabeculoplasty inflammation of the anterior segment of the eye, and for the inhibition of intra-operative miosis

Related Submissions: [redacted]

PRECLINICAL STUDIES

PHARMACOLOGY

A. General Pharmacology

1. Anti-inflammatory, antierythmic, analgesic & antipyretic effects of FBP, inhibition of prostaglandin synthesis & acid-induced capillary permeability (mouse peritoneum) by FBP, effects on body temperature (rat), CNS (conscious mouse) & cardiovascular system (anesthetized cat), and drug metabolism (mouse, rat, dog, baboon & man) were studied by Boots and were submitted in connection with [redacted] (tablets & syrup for oral use) to HFN-150. These studies were reviewed by Mr. Whitehurst & Dr. Richman (HFN-150 Pharm. Rev. dated 8/29/79).

2. The following studies were submitted in connection with [redacted] (Original Submission, June 1978) for FBP ophth. sol'n & suspension and were reviewed by Mr. Whitehurst & Dr. Richman: Anti-inflammatory activity of FBP; vehicle pH effects and evaluation of 0.01% solution (1977).

B. Ocular Pharmacology

The following studies have previously been submitted [redacted] by the applicant, and have been reviewed by Mr. Whitehurst.

1. One-day irritation study on 1.0% FBP (Allergan)
2. Ocular evaluation of FBP in rabbits on immunogenic uveitis and herpes keratitis (Allergan)

The following studies, all performed by the applicant, have previously been submitted as amendments to [redacted] and have been reviewed by the present reviewer.

1. Anti-inflammatory activity of sodium FBP (0.01%, 0.03% or 0.1%) in model adjuvant-induced uveitis
2. FBP vs. prednisolone in adjuvant-induced uveitis

ADME STUDIES

A. Drug Kinetics: (Done by Boots and reviewed by Mr. Whitehurst.)

"The metabolism of Flubiprofen has been studied in mouse, rat, dog, baboon and man. This drug is rapidly absorbed in all these species, peak serum concentration was observed at 1 to 3 hours.

The elimination of unchanged Flurbiprofen was rapid (half-life 3-4 hours) in all animal except the dog, half life 6 1/2-12 hours). Elimination is thougnt to be biphasic, a rapid elimination during the first 3-6 hours and then a slower elimination lasting to 24 hours. The drug is eliminated mainly via the urine. (70-80%). There is no accumulation of the drug in any of the animal species except the rat. In the rat, the drug accumulates in the liver, kidney, large intestine, adrenal and thyroid. Flurbiprofen penetrates the tissues of the fetuses in pregnant rats and rabbits. The major metabolite of Flurbiprofen found in the urine of man is 2-(2-fluoro-4'-hydroxy-4 biphenylyl) propionic acid."

B. The following studies, done by Allergan, were submitted previously as amendments to [redacted] and have been reviewed by the present reviewer [redacted]:

1. FBP absorption in ocular tissues (rabbits; 1979)
2. Systemic metabolism & elimination of ^{14}C-FBP in rabbits after ocular or IV treatment (1980)
3. Absorption, distribution & metabolism of FBP in aphakic rabbit eyes (1981)
4. FBP metabolism in ocular tissues (1980)
5. Systemic metabolism & elimination of ^{14}C-FBP in rabbits after ocular or IV treatment (1980)
6. Systemic metabolism & elimination of FBP in guinea pigs following ocular or IV administration (1980)

C. The following studies are new to this NDA and are reviewed here (all performed by the applicant):

1. Ocular & Systemic Bioavailability of Ophthalmic FBP (1984)

Methods: Anesthetized albino F rabbits received FBP doses intracamerally (10 ul of 0.3% or 0.6% FBP), topically (50 ul of 0.15% or 0.3% FBP, i.e., 75 or 150 ug), and IV (6 or 208 ug of FBP) at 2 to 4-week intervals. Aqueous humor & plasma were used as the sampling compartments.

Results: After IV admin., plasma clearance values of FBP were 6.77 ml/min. & 7.87 ml/min. after 6 mg & 208 ug IV doses, respectively, indicating no dose-dependent disposition kinetics over a 30-fold dose range. The systemic & ocular distribution half-lives of FBP were 12 min. & 20 min., respectively. The plasma elimination half-life after IV admin. was 74 min. and the aq. humor elimination half-life after intracameral injection was 93 min. The latter was approx. equal to the turnover rate of aq. humor. The aq. humor levels of FBP were approx. 100x lower than plasma levels at corresponding times.

No FBP was detected in the contralateral eye when the drug was delivered intracamerally in the right eye, and no sig. breakdown of the blood-aq. humor barrier was reported.

The extent of absorption of FBP when applied topically to the eyes was not proportionally dose-related. About 7% of a 150 ug topical dose was found to be absorbed ocularly compared with 10% absorption of a 75 ug dose. A major portion of the topically applied dose (74%) entered systemic circulation.

2. Absorption & Distribution of Ocularly Applied [^{14}C]-FBP in Pretreated Rabbits

Methods: Distribution of [^{14}C] radiolabeled FBP in albino rabbit (NZ, F) ocular tissues was investigated following 7 consecutive days of ocular pretreatment with nonradioactive FBP (0.03%, 50 ul q.i.d.). After one additional treatment with radioactive FBP, ocular tissues were obtained at various intervals from euthanized animals and radioactivity (RA) was determined.

Results: Increasing RA was found in the first hr after topical application in aq. humor, cornea, conjunctiva, choroid, retina, optic nerve & sclera. There was a gradual decrease in RA after this, but it was still detectable at 6 hrs.

Table I (attached) shows the percent of the original dose present in each ocular tissue. Cornea showed the highest drug uptake (3.8% of the dose at 30 min. & 4.37% at 1 hr after drug application).

Comparisons by t-test analysis of drug absorbed by individual ocular tissues at each time interval between the 7-day pretreated & non-pretreated animals indicated that drug distribution was sig. different in ciliary body, iris, nictitating membrane & sclera (higher conc'ns in pretreated animals). Since the aq. humor elimination rates were similar in both groups (0.005 m^{-1}), there was apparently some accumulation of drug in these vascularized tissues.

3. Effects of 48-Hour & 96-Hour Pretreatment on Ocular Penetration of ^{14}C-FBP

Methods: A total of 8 rabbits were ocularly treated in both eyes with 50 uT of 0.03% [^{14}C]-FBP in vehicle 5707X. Four animals received

Results: After IV admin., plasma clearance values of FBP were 6.77 ml/min. & 7.87 ml/min. after 6 mg & 208 ug IV doses, respectively, indicating no dose-dependent disposition kinetics over a 30-fold dose range. The systemic & ocular distribution half-lives of FBP were 12 min. & 20 min., respectively. The plasma elimination half-life after IV admin. was 74 min. and the aq. humor elimination half-life after intracameral injection was 93 min. The latter was approx. equal to the turnover rate of aq. humor. The aq. humor levels of FBP were approx. 100x lower than plasma levels at corresponding times.

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3. Effects of 48-Hour & 96-Hour Pretreatment on Ocular Penetration of ^{14}C-FBP

Methods: A total of 8 rabbits were ocularly treated in both eyes with 50 ul of 0.03% [^{14}C]-FBP in vehicle 57°7X. Four animals received

drug applications 4x/day for 48 hrs while the other 4 were treated for 96 hrs (4x/day). On the morning following the last dose, each animal received an additional 50 ul to each eye 30 min. prior to sacrifice. Two rabbits from each gp received a 1 ml saline wash in both eyes following sacrifice. RA was determined in aq. humor and various ocular tissues, and was expressed as ng of original drug/g of tissue.

Results: Conc'ns of RA material in ocular tissues expressed as ng/g tissue are shown in Table 2 (attached) and as percent of original dose in Table 3 (also attached). Corneal conc'ns appeared the highest in both gps at both time intervals.

No sig. differences in FBP conc'n were noted between washed & unwashed ocular tissues or between pretreated 48 or 96-hr gps. Sig. differences in RA were found between tissues obtained from repeated dose vs. single dose gps. The last observation suggested that a therapeutically higher ocular conc'n, if needed, might be achieved by a multiple dosing or pretreatment regimen.

4. Absorption & Distribution of FBP in Ocular Tissue under Multiple Dosing Regimen

Methods:

a) One gp of 4 F NZ albino rabbits was treated ocularly in one eye with a 50 ul dose every 2 hrs (total of 6 times). The following day, each rabbit received 6 additional treatments at 30-min. intervals for a final total dose of 600 ul each prior to sacrifice. The contralateral eye in each test animal remained untreated. The rabbits were killed 30 min. following the final application. The RA in each ocular tissue was then determined.

b) Two animals/group were used in this study. Group 1 received one 50 ul application to each eye, Group 2 received 3 applications at 30-min. intervals and Group 3 received 6 applications at 30-min. intervals, of 0.03% [^{14}C]-FBP. Thirty min. after the last dose, the animals were sacrificed & various ocular tissues examined for RA.

Results:

a) The cornea showed the highest level of all ocular tissues with a conc'n of 28.33 ug/g. This was followed by conjunctiva (6.406 ug/g) & sclera (5.653 ug/g). In the anterior segment of the eye, the iris showed the highest tissue level (3.046 ug/g) followed by the aq. humor (2.041 ug/g) & ciliary body (1.601 ug/g). Vitreous humor, lens & optic nerve had very low activities.

b) Conc'n of RA materials in ocular tissue expressed as ng/g of FBP after 1, 3 & 6 multiple dosings are presented in Table 4 (attached). Again, the highest conc'n of the drug was found in the cornea, which was followed by the conjunctiva & sclera. A plateau in drug conc'n was reached after 3 consec. application, 30 min. apart.

Stat. sig. differences in RA were noted in samples following 1 & 3 dosings, but not after 3 & 6 dosings.

TOXICOLOGY

A. Acute Toxicity: The following studies have already been reviewed in connection with [redacted] (Pharm. Revs.).

1. LD_{50} in mice, rats, dogs & baboons by various route (Boots)
2. One-day irritation study (1% FBP) by Allergan
3. Acute (1-day) multiple-dose eye irritation study (0.1% FBP) by Allergan

The following new studies have been submitted in this NDA (all performed by Allergan).

1. One-day Acute Eye Toxicity Study on Flurbiprofen Solutions No. 5797X-5609 & No. 5927X-5611D (clinical return samples)

This study could not be reviewed because the compositions of the formulations have not been given, and part of the report is illegible (pp. 105062-105063).

2. One-day Acute Eye Toxicity Study on Sodium FBP 0.1% solution No. 6965X-001 & 0.03% Solution No. 6970X-001

Ocular effects in NZ rabbits (3/group) of thee above formulations were evaluated following one day of multiple topical instillations. One drop of the test material was instilled 16 times in the left eye (dosing interval has not been given) in 24 hrs. Contralateral eyes remained untreated for control purpose.

Results: The sol'ns were found to be nontoxic, as no ocular reactions were noted at slit lamp exams following the last instillation.

B. Subacute & Chronic Toxicity Studies

1. The following studies, reviewed by Mr. Whitehurst, were submitted in connection with the Original IND.

Allergan

a) 21-day subacute toxicity on FPB
b) 21-day subacute toxicity on FBP suspension. No histological analyses were performed.

Boots

c) 30-day oral toxicity in rats
d) 30-day oral toxicity in cats
e) 30-day oral toxicity in dogs
f) 6-month oral toxicity in mice
g) 6-month oral toxicity in rats

Stat. sig. differences in RA were noted in samples following 1 & 3 dosings, but not after 3 & 6 dosings.

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a) 21-day subacute toxicity on FPB
b) 21-day subacute toxicity on FBP suspension. No histological analyses were performed.

Boots

c) 30-day oral toxicity in rats
d) 30-day oral toxicity in cats
e) 30-day oral toxicity in dogs
f) 6-month oral toxicity in mice
g) 6-month oral toxicity in rats

h) 2-year oral toxicity in rats
i) 30-day Oral Toxicity in baboons

2. The following preclinical studies have been reviewed by this reviewer.

a) 21-day subacute ocular toxicity (Allergan)
b) 30-day subacute oral toxicity in rats (preliminary)
c) 30-day subacute oral toxicity in rats (Boots)
d) 6-month oral toxicity in rats (Boots)
e) Carcinogenicity test in mice (Boots)
f) One-year topical ocular toxicity in rabbits (Allergan)

C. Reproduction

All studies were performed either by Boots or Laboratories Dacour. These studies were submitted in [redacted] (reviewed by Mr. Whitehurst) and 14,396 (reviewed by this reviewer).

1. Teratogenicity in mice (Segment II)
2. Teratogenicity in rats (Segments I & II)
3. Perinatal & postnatal effect of FBP treatment in rats (Segment III)
4. Comparative effects of FBP, flufenamic acid & indomethacin on pup birth when administered to pregnant rats
5. Teratogenicity in rabbits (Segment II)

MICROBIOLOGY

The preservative efficacy of 0.03% FBP ophth. sol'n containing 0.005% thimerosal was tested in vitro against Staphylococcus, Serratia, Pseudomonas, E. coli, Candida albicans & Aspergillus niger, and was reported to be stable for 48 mos. at 23°C.

EVALUATION

Most of the general pharmacology and systemic toxicology (oral) studies performed in animals were submitted to HFN-150 in Boots' [redacted] The Original [redacted] submission for FBP ophthalmic solution was also made to HFN-150 and was reviewed by Mr. Whitehurst. The rest of the studies enumerated here have been reviewed by this reviewer.

The applicant initially had studied a 0.1% FBP solution which had chlorobutanol as the preservative. Later the formulation was modified to contain 0.03% FBP and the preservative was changed to thimerosal.

Flurbiprofen (FBP), a non-steroidal anti-inflammatory agent (NSAID), has been marketed for oral use in various countries throughout the world (but not in the USA), and is indicated for treatment of rheumatoid disease, osteoarthrosis, ankylosing spondolytis & allied conditions. Thus, its clinical usefulness is well established. However, no NSAID has yet been approved in the USA for ophthalmic indications.

The topical (ocular) anti-inflammatory activity of FBP was assessed in 3 animal models: experimental immunogenic uveitis, endotoxin-induced inflammation and a reverse arthus model of inflammation. Although the drug showed significant inhibition of inflammatory response at doses of 0.03% or greater concentration, there was no consistent dose-response relationship. Thus, in one study, 0.1% FBP was more effective than a 1.0% solution. In another study, a dose-dependent increase in activity was seen, whereas in a third study, there were no appreciable differences in activity among the 3 different concentrations of FBP. On a weight basis, FBP sodium was 4-10 times more effective (depending on concentration used) than prednisolone acetate in reducing uveitis parameters.

The ocular ADME studies were performed in rabbits with normal and aphakic eyes. In normal eyes, by far the largest fraction of the dose was absorbed by the cornea (> 77% of the absorbed dose), followed by aqueous humor and choroid/retina. In contrast, in the aphakic eyes, although the cornea still showed the greatest absorption, the iris had more radioactivity than either aqueous humor or choroid/retina. The elimination half-lives from ocular tissues (4-5 hours), however, did not differ significantly. The rates of drug elimination from the aqueous humor, determined from these studies, were found to be much slower than the rates of aqueous humor turnover, indicating some sequestration of drug in ocular tissues. In both groups, about 5% of the dose was absorbed by the ocular tissues, the rest being absorbed systemically. Ocular bioavailability was found to be almost independent of the doses used.

In both the ocularly and IV treated rabbits, systemically absorbed radioactivity (drug metabolites) was excreted exclusively through the kidneys Excretory products consisted of a major metabolite (66-77%) and the unchanged FBP (19-25%). Although not examined, similar metabolism would also be expected in aphakic rabbits, since no metabolism was found to occur in ocular tissues either in vivo or in vitro. The major metabolite in the urine of man was identified as 2-(2-fluro-4'-hydroxy-4-biphenyl) propionic acid.

There was no significant differences in plasma half-lives of radioactivity between the IV and ocularly treated rabbits. Ocular pretreatment with FBP, however, increased the $t_{1/2}$ considerably. Furthermore, it was shown that drug concentration in ocular tissues could be increased by ocular pretreatment schedule, which may have some clinical usefulness.

Guinea pigs, pretreated or nonpretreated, differed considerably from rabbits in both ocular absorption and metabolism. Excretion was by both fecal & urinary routes and the parent compound represented 85-90% of the total urinary radioactivity.

Systemic absorption and elimination have been examined in mice, rats, dogs, baboon & man. The absorption of orally administered drug was rapid in all species. On repeated oral dosing, no tissue accumulation was reported in any species except the rat (liver & kidney).

This is one of the NDAs for which most of the systemic preclinical toxicity studies have been submitted to another division (HFN-150). However, all the ocular toxicity studies and some acute, subacute and chronic toxicity studies,

along with summaries of reproduction studies and a mouse carcinogenicity test had been submitted to this division ([redacted]), and have been reviewed

On the basis of oral LD_{50} in rats, acutely the drug substance may be classified as slightly toxic.

The present clinical formulation has thimerosal as the preservative. Earlier formulations were used in some toxicity studies. No ocular reactions, discomfort or irritation have been reported with the present formulation.

In a one-year ocular (topical) toxicity study in rabbits, all the significant adverse effects seen grossly seemed to have no dose-response relationship, and were present in control as well as treated groups. Histopathological exams, however, revealed a significant finding, namely "status spongiosis" (described as "clear, round, empty vacuoles" formed within the optic nerve or the CNS). At both interim and final sacrifices, the incidences of this lesion in the optic nerves were 100% in all but the low-dose groups, and both eyes were affected. At interim (90-day) sacrifice only, the incidence of vacuoles in the CNS, however, showed dose-related increase. While the incidence was 20% in the control group, rates as high as 83% were reported in the fore and hind brains of the drug-treated animals, and the incidence increased in a dose-related manner. Since there was no associated gliasis or inflammation and the vacuoles were generally empty, the pathologist concluded that the lesions were artefactual and "possibly related to fixation". Although this explanation appears to be reasonable, the presence of a definite pattern of dose-response relationship in the case of CNS lesions indicated further examination of this effect. I had, therefore, recommended a repeat of the 90-day ocular study, but utilizing only two groups of animals - untreated controls and the high-dose group ([redacted] Pharm. Rev. dated 11/7/84). I had reported my recommendation again in my review of NDA 19-404 (amendment [redacted]). I understand that Mr. Linkous has been assured by Allergan that the study is ongoing and is being carried out under conditions to minimize artefactuality.

In subacute and chronic (6-month) oral toxicity studies in rats, severe GI ulceration, anemia and changes in lymph nodes, livers, spleen and kidneys were reported. A "no effect" dose in this species was found to be 1 mg/kg/day.

Reproduction studies in mice, rats and rabbits indicated that flurbiprofin adversely affects the general reproduction performances of these animals. Although the drug was fetotoxic, it appeared not to have any teratogenic effects in these species.

Increased incidence of lymphosarcoma was reported in a mouse carcinogenicity test. This and other long-term studies have been reviewed in-depth by Dr. Coulter of HFN-150 in connection with NDA [redacted]. He told me that these NDAs now have "approvable" status. Also, the ophthalmic preparation is indicated, at present, only for short-term usage.

RECOMMENDATION

Final

Syed N. Alam, Ph.D.

cc: Orig. NDA
HFN-815
HFN-815/MO
CSO
HFN-340
HFN-815/SNAlam/smc/7/18/85
R/d init.by:JMDavit
0022p

Attachments (4)

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-404 Amendment,

Date Review Completed: 8/2/85

Applicant: Allergan Pharmaceuticals, Irvine, CA

Drug: Flurbiprofen (0.03%) Ophthalmic Solution

Category: Non-steroidal anti-inflammatory

Indication: Treatment of post-operative & post-laser trabeculoplasty inflammation and for inhibition of intra-operative miosis

Related Submission:

Preclinical Studies: No new studies have been submitted.

Comments:

"Status spongiosis" described as "clear, round empty vacuoles within optic nerve neural substance" or scattered throughout neuropil of the central nervous system" was seen in a one-year topical ocular toxicity study in rabbits submitted earlier (Pharm. Rev. dated 11/7/84). At interim (3-mo.) sacrifice, the incidence of this lesion was found to be dose-related for all parts of the brain. I had, therefore, recommended that the applicant perform a 90-day toxicity study comprised only of untreated control and high-dose groups, to determine if the observed "status spongiosis" was actually an artefact, as claimed by the pathologist. Instead of performing such a study, the applicant (in a subsequent amendment [redacted] submitted results showing 9/12 rabbits from an unrelated untreated group had similar brain lesions. Pursuant to a telcon, I was provided with a desk copy of a publication (J. Histotech. Vol. 5, # 4, p. 171, 1982) which reported such artefactual brain lesions when rat brain tissues were held in 70% alcohol for 48 hrs for fixation, but none when 10% neutral buffered formalin was used. A copy of a letter from the pathologist (Dr. Culbertson) to the applicant was also provided, and is attached to this review. I, therefore, had recommended that the study be performed under conditions described in the paper to avoid artefactual formation of the brain vacuoles. Apparently, in the rabbit experiment, vacuoles were observed even though the brain tissues were actually fixed in 10% formalin.

In this submission, the applicant has submitted histopathologic findings for tissues from 8 other animal studies performed with 6 different ophthalmic preparations (hydroxyamphetamine, levobunolol HCl, prednisolone acetate, oxymetazoline HCl, fluorometholone or cimetadine/pyrilamine) & 2 dermatologic preparations (erythromycin/azone or a broad spectrum sunscreen lotion). In all cases, "status spongiosis" was seen either in the optic nerve or the CNS, or both. In the untreated controls in these experiments, the incidence varied from sporadic to 100% occurrence in the CNS and from none to about 100% in the optic nerves. Strangely, almost all animals from all groups in the 6-month

chronic dermal study in rats with erythromycin/azone topical sol'n had "vacuolation of the white matter in spinal cord and brain tissues" (Allergan, study # 1228A-0294-1), whereas the applicant stated that "flurbiprofen has been studied systemically at much higher doses" than that used in ocular study "in baboons, dogs, rats & mice without any status spongiosis or related matter reported" (cover letter, dated 7/15/85). However, in the 1-year flurbiprofen ocular study (# 1334-79,0119-748), the initial report suggested that there was a dose-related increase in "status spongiosis" in the CNS, and the increase appeared to be significantly greater than in controls.

Because of this last finding, newly cut sections of tissues from the animals sacrificed at 90 days were examined & re-evaluated by the applicant's pathologist. The following lesion incidences were reported.

Tissue	Group I (Low Dose)	Group II (Mid Dose)	Group III (High Dose)	Group IV (Control)
Forebrain	3/6 (50%)	0/6 (0%)	3/5 (50%)	3/5 (60%)
Midbrain	3/6 (50%)	4/6 (66%)	5/6 (83%)	5/5 (100%)
Hindbrain	6/6 (100%)	6/6 (100%)	6/6 (100%)	5/5 (100%)

It is obvious from the table that in all cases the incidence in the controls was more than that in the treated animals. These discrepancies in the results have been explained by the pathologist by the following statement: "this change may be found in most if not all such tissues if one diligently searches it out." The pathologist apparently now uses the term "white matter vacuolation" rather than "status spongiosis", which has pathological significance. Based on the data in this submission, I tend to agree with the pathologist's conclusion that the observed vacuoles in brain tissues were most likely artefacts produced during processing of tissue samples. An additional toxicity study is not necessary.

Recommendation:

Based on the new information submitted in this amendment, I find the application approvable.

Syed N. Alam, Ph.D.

cc: Orig. ~~NDA~~ 2 + 8/16/85
HFN-815
HFN-815/MO
CSO
HFN-340
HFN-815/SNAlam/smc/8/12/85
R/d init.by:JMDavitt
0047p
ATTACHMENTS