CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-700 / S-019
20-811 / S-003

Trade Name: **Acular**

Generic Name: **Ketrolac tromethamine ophthalmic solution**

Sponsor: **Allergan, Inc.**

Approval Date: **February 8, 2002**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-700 / S-019
20-811 / S-003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-700 / S-019
20-811 / S-003

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-700/S-019
NDA 20-811/S-003

Allergan, Inc.
Attention: Elizabeth Bancroft
Senior Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Ms. Bancroft:

Please refer to your supplemental new drug applications dated June 18, 2001, received June 19, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA 19-700/S-019	Acular (ketorolac tromethamine ophthalmic solution) 0.5% Sterile Ophthalmic Solution
NDA 20-811/S-003	Acular PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free Sterile Ophthalmic Solution

We acknowledge receipt of your submissions dated July 26, August 27, and October 2, 2001, and January 17 and 22, 2002.

These supplemental new drug applications propose a change in the wording of the pediatric section of the package inserts.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted January 22, 2002).

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 19-700/S-019, and NDA 20-811/S-003." Approval of these submissions by FDA is not required before the labeling is used.

We recommend that the package insert of Acular PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free Sterile Ophthalmic Solution, contain information in the How Supplied section on the target fill volume for each container size, and the color and type of plastic for the vial.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have fulfilled the pediatric study requirement at this time.

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to the appropriate NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of each drug product when they are available.

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

If you have any questions, call Raphael Rodriguez, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wiley Chambers
2/8/02 01:42:18 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-700 / S-019
20-811 / S-003

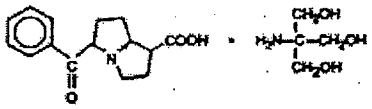
LABELING

ACULAR®
(ketorolac tromethamine ophthalmic solution)
0.5%
Sterile

ALLERGAN

DESCRIPTION

ACULAR® (ketorolac tromethamine ophthalmic solution) is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs) for ophthalmic use. Its chemical name is (±)-5-benzoyl-2, 3-dihydro-1H pyrrolizine-l-carboxylic acid compound with 2-amino-2-(hydroxymethyl)-1 ,3-propanediol (1:1) and it has the following structure:



ACULAR® ophthalmic solution is supplied as a sterile isotonic aqueous 0.5% solution, with a pH of 7.4. ACULAR® ophthalmic solution is a racemic mixture of R-(+) and S-(-)-ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. The pKa of ketorolac is 3.5. This white to off-white crystalline substance discolors on prolonged exposure to light. The molecular weight of ketorolac tromethamine is 376.41. The osmolality of ACULAR® ophthalmic solution is 290 mOsmol/kg.

Each mL of ACULAR® ophthalmic solution contains: Active: ketorolac tromethamine 0.5%. Preservative: benzalkonium chloride 0.01 %. Inactives: edetate disodium 0.1 %; octoxynol 40; sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH; and purified water.

CLINICAL PHARMACOLOGY

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory, and anti-pyretic activity. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis. Ketorolac tromethamine given systemically does not cause pupil constriction.

Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, 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.

Two drops (0.1 mL) of 0.5% ACULAR® ophthalmic solution instilled into the eyes of patients 12 hours and 1 hour prior to cataract extraction achieved measurable levels in 8 of 9 patients' eyes (mean ketorolac concentration 95 ng/mL aqueous humor, range 40 to 170 ng/mL). Ocular administration of ketorolac tromethamine reduces prostaglandin E_2 (PGE_2) levels in aqueous humor. The mean concentration of PGE_2 was 80 pg/mL in the aqueous humor of eyes receiving vehicle and 28 pg/mL in the eyes receiving ACULAR® 0.5% ophthalmic solution.

One drop (0.05 mL) of 0.5% ACULAR® ophthalmic solution was instilled into one eye and one drop of vehicle into the other eye TID in 26 normal subjects. Only 5 of 26 subjects had a detectable amount of ketorolac in their plasma (range 10.7 to 22.5 ng/mL) at day 10 during topical ocular treatment. When ketorolac tromethamine 10 mg is administered systemically every 6 hours, peak plasma levels at steady state are around 960 ng/mL.

Two controlled clinical studies showed that ACULAR® ophthalmic solution was significantly more effective than its vehicle in relieving ocular itching caused by seasonal allergic conjunctivitis.

Two controlled clinical studies showed that patients treated for two weeks with ACULAR® ophthalmic solution were less likely to have measurable signs of inflammation (cell and flare) than patients treated with its vehicle.

Results from clinical studies indicate that ketorolac tromethamine has no significant effect upon intraocular pressure; however, changes in intraocular pressure may occur following cataract surgery.

INDICATIONS AND USAGE

ACULAR® ophthalmic solution is indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis. ACULAR® ophthalmic solution is also indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

CONTRAINDICATIONS

ACULAR® ophthalmic solution is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

WARNINGS

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

With some nonsteroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS

General: All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation . These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post surgery may increase patient risk for the occurrence and severity of corneal adverse events.

It is recommended that ACULAR® ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Information for Patients: ACULAR® ophthalmic solution should not be administered while wearing contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Ketorolac tromethamine was not carcinogenic in rats given up to 5 mg/kg/day orally for 24 months (151 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals) nor in mice given 2 mg/kg/day orally for 18 months (60 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals).

Ketorolac tromethamine was not mutagenic *in vitro* in the Ames assay or in forward mutation assays. Similarly, it did not result in an *in vitro* increase in unscheduled DNA synthesis or an *in vivo* increase in chromosome breakage in mice. However, ketorolac tromethamine did result in an increased incidence in chromosomal aberrations in Chinese

hamster ovary cells.

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 272 and 484 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals.

Pregnancy:
Teratogenic Effects: Pregnancy Category C. Ketorolac tromethamine, administered during organogenesis, was not teratogenic in rabbits or rats at oral doses up to 109 times and 303 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis assuming 100% absorption in humans and animals. When administered to rats after Day 17 of gestation at oral doses up to 45 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals, ketorolac tromethamine resulted in dystocia and increased pup mortality. There are no adequate and well-controlled studies in pregnant women. ACULAR® ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ACULAR® ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers: Caution should be exercised when ACULAR® ophthalmic solution is administered to a nursing woman.

Pediatric Use: Safety and efficacy in pediatric patients below the age of 3 have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by up to 40% of patients participating in clinical trials.

Other adverse events occurring approximately 1 to 10% of the time during treatment with ketorolac tromethamine ophthalmic solutions included allergic reactions, corneal edema, iritis, ocular inflammation, ocular irritation, superficial keratitis and superficial ocular infections.

Other adverse events reported rarely with the use of ketorolac tromethamine ophthalmic solutions included: corneal infiltrates, corneal ulcer, eye dryness, headaches, and visual disturbance (blurry vision).

Clinical Practice: The following events have been identified during postmarketing use of ketorolac tromethamine ophthalmic solution 0.5% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical ketorolac tromethamine ophthalmic solution 0.5%, or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown (see PRECAUTIONS, General).

DOSAGE AND ADMINISTRATION

The recommended dose of ACULAR® ophthalmic solution is one drop (0.25 mg) four times a day for relief of ocular itching due to seasonal allergic conjunctivitis.

For the treatment of postoperative inflammation in patients who have undergone cataract extraction, one drop of ACULAR® ophthalmic solution should be applied to the affected eye(s) four times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period.

ACULAR® ophthalmic solution has been safely administered in conjunction with other ophthalmic medications such as antibiotics, beta blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics.

HOW SUPPLIED

ACULAR® (ketorolac tromethamine ophthalmic solution) is supplied sterile in opaque white LDPE plastic bottles with white droppers with gray high impact polystyrene (HIPS) caps as follows:

3 mL in 6 mL bottle **NDC** 0023-2181-03
5 mL in 10 mL bottle **NDC** 0023-2181-05
10 ml in 10 mL bottle **NDC** 0023-2181-10

Store at room temperature 15°C -30°C (59°F- 86°F) with protection from light.

Rx only

U.S. Patent Nos.: 4,454,151; 5,110.493; and 5,414,011

ACULAR® (a registered trademark of SYNTEX (U.S.A.) Inc.) is manufactured and distributed by ALLERGAN under license from its developer, SYNTEX (U.S.A.) Inc., Palo Alto, California, U.S.A.

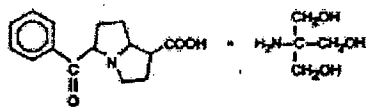
Revised January 2002

Formulation Number: 08344X

ACULAR® PF
(ketorolac tromethamine ophthalmic solution) 0.5%
Preservative-Free
Sterile ALLERGAN

DESCRIPTION

ACULAR® PF (ketorolac tromethamine ophthalmic solution) Preservative-Free is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs) for ophthalmic use. Its chemical name is (±)-5-benzoyl-2, 3-dihydro-1H pyrrolizine-1-carboxylic acid compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) and it has the following structure:



ACULAR® PF is a racemic mixture of R-(+) and S-(-)-ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. The pKa of ketorolac is 3.5. This white to off-white crystalline substance discolors on prolonged exposure to light. The molecular weight of ketorolac tromethamine is 376.41. The osmolality of ACULAR® PF is 290 mOsmol/kg.

Each ml of ACULAR® PF contains: Active ingredient: ketorolac tromethamine 0.5%. Inactives: sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH to 7.4; and purified water.

CLINICAL PHARMACOLOGY

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory, and anti-pyretic activity. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis. Ketorolac tromethamine given systemically does not cause pupil constriction.

One drop (0.05 mL) of ketorolac tromethamine (preserved) was instilled into one eye and one drop of vehicle into the other eye TID in 26 normal subjects. Only 5 of 26 subjects had a detectable amount of ketorolac in their plasma (range 10.7 to 22.5 ng/mL) at day 10 during topical ocular treatment. When ketorolac tromethamine 10 mg is administered systemically every 6 hours, peak plasma levels at steady state are around 960 ng/mL.

In two double-masked, multi-centered, parallel-group studies, 340 patients who had undergone incisional refractive surgery received ACULAR® PF or its vehicle QID for up to 3 days. Significant

differences favored ACULAR® PF for the treatment of ocular pain and photophobia. Results from clinical studies indicate that ketorolac tromethamine has no significant effect upon intraocular pressure.

INDICATIONS AND USAGE

ACULAR® PF ophthalmic solution is indicated for the reduction of ocular pain and photophobia following incisional refractive surgery.

CONTRAINDICATIONS

ACULAR® PF ophthalmic solution is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

WARNINGS

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

With some nonsteroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS

General: All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. . Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation . These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post surgery may increase patient risk for the occurrence and severity of corneal adverse events.

It is recommended that ACULAR® PF ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Information for Patients: ACULAR® PF should not be administered while wearing contact lenses.

The solution from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration. To avoid contamination, do not touch tip of unit-dose vial to eye or any other surface.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Ketorolac tromethamine was not carcinogenic in rats given up to 5 mg/kg/day orally for 24 months (151 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals) nor in mice given 2 mg/kg/day orally for 18 months (60 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals).

Ketorolac tromethamine was not mutagenic *in vitro* in the Ames assay or in forward mutation assays. Similarly, it did not result in an *in vitro* increase in unscheduled DNA synthesis or an *in vivo* increase in chromosome breakage in mice. However, ketorolac tromethamine did result in an increased incidence in chromosomal aberrations in Chinese hamster ovary cells.

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 272 and 484 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals.

Pregnancy:
Teratogenic Effects: Pregnancy Category C. Ketorolac tromethamine, administered during organogenesis, was not teratogenic in rabbits or rats at oral doses up to 109 times and 303 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis assuming 100% absorption in humans and animals. When administered to rats after Day 17 of gestation at oral doses up to 45 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals, ketorolac tromethamine resulted in dystocia and increased pup mortality. There are no adequate and well-controlled studies in pregnant women. ACULAR® PF ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ACULAR® PF ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers: Caution should be exercised when ACULAR® PF is administered to a nursing woman.

Pediatric Use: Safety and efficacy in pediatric patients below the age of 3 have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by approximately 20% of patients participating in clinical trials.

Other adverse events occurring approximately 1 - 10% of the time during treatment with ketorolac tromethamine ophthalmic solutions included allergic reactions, corneal edema, iritis, ocular inflammation, ocular irritation, superficial keratitis, and superficial ocular infections.

Other adverse events reported rarely with the use of ketorolac tromethamine ophthalmic solutions include: corneal infiltrates, corneal ulcer, eye dryness, headaches, and visual disturbance (blurry vision).

Clinical Practice: The following events have been identified during postmarketing use of topical ketorolac tromethamine ophthalmic solution 0.5% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical ketorolac tromethamine ophthalmic solution 0.5%, or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown (see PRECAUTIONS, General)

DOSAGE AND ADMINISTRATION

The recommended dose of ACULAR® PF is one drop (0.25 mg) four times a day in the operated eye as needed for pain and photophobia for up to 3 days after incisional refractive surgery.

HOW SUPPLIED

ACULAR® PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free is available as a sterile solution supplied in single-use vials as follows:

ACULAR® PF 12 Single-Use Vials 0.4 mL each
NDC 0023-9055-04

Store ACULAR® PF between 15°C - 30°C (59°F - 86°F) with protection from light.
Rx only

U.S. Patent Nos.: 4,454,151; 5,110,493; and 5,414,011.

ACULAR® is a registered trademark of SYNTEX (U.S.A.) Inc. ACULAR® PF is manufactured and distributed by ALLERGAN under license from its developer, SYNTEX (U.S.A.) Inc., Palo Alto, California, U.S.A.

Revised January 2002

8718X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-700 / S-019
20-811 / S-003

MEDICAL REVIEW(S)

Medical Officer's Review

Supplemental NDA 19-700/S-019
&
Supplemental NDA 20-811/S-003

Tradename:	Acular (ketorolac tromethamine 0.5%) Acular PF (ketorolac tromethamine 0.5%)
Sponsor:	Allergan 2525 Dupont Drive P.O. Box 19534 Irvine, California 92623-9534
Proposed Indication:	Pediatric Exclusivity (≥ 3 years old)
Date of Submission:	June 19, 2001
Date of Review:	August 27,2001

Table of Contents

Executive Summary

I. Recommendations

A. It is recommended that supplemental NDA 19-700/S-019 and NDA 20-811/S-003 be approved. The sponsor adequately followed all requirements set forth in the pediatric request. The application supports the safety and tolerability of Acular (ketorolac tromethamine ophthalmic solution 0.5%) in the pediatric population ≥ 3years of age for the treatment of ocular itching caused by seasonal allergic conjunctivitis and for post-surgical inflammation following cataract surgery. The efficacy may be extrapolated down from older individuals.

II. Summary of Clinical Findings

A. Overview of clinical program

Acular (ketorolac tromethamine ophthalmic solution 0.5%) is a topical nonsteroidal anti-inflammatory drug (NSAID) indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis and is indicated for post-surgical inflammation following cataract surgery. Acular PF is the preservative free formulation of ketorolac tromethamine ophthalmic solution 0.5% and is indicated for the pain and photophobia following incisional refractive surgery. Ketorolac's most common adverse events include transient burning and stinging upon instillation. These events are reported by up to 40% of subjects using ketorolac and up to 20% of subjects using the preservative free formulation.

A written request for the use of Acular in the pediatric population was sent to the sponsor on May 10, 2000, to evaluate the safety and tolerability in this population. It was the agency's view that efficacy data could be reliably extrapolated from the existing clinical database. It was also determined by the agency that safety data gathered from evaluating the preserved form of this product would yield adequate information that could be applied to the non-preserved formulation. Therefore, this submission contains clinical data which assesses the safety and tolerability of Acular (ketorolac tromethamine ophthalmic solution 0.5%) only.

B. Efficacy

Efficacy was not evaluated as part of this submission. It is the agency's view that efficacy data can be reliably extrapolated from the existing clinical database.

C. Safety

There were no significant differences between subjects receiving Ketorolac, and subjects receiving vehicle, in any of the measured safety parameters including adverse events, subject tolerability to treatment, visual acuity measurements and biomicroscopy findings, during the

course of the study. Ketorolac has an acceptable safety profile for use in a pediatric population ≥3 years of age, with a one drop per eye, q.i.d dosing regimen.

D. Dosing – N/A
E. Special Populations – N/A

Clinical Review

I. Introduction and Background

Tradename:	Acular (ketorolac tromethamine ophthalmic solution) 0.5%
Sponsor:	Allergan 2525 Dupont Drive P.O. Box 19534 Irvine, California 92623-9534
Pharmacologic Category:	Non-steroidal anti-inflammatory
Proposed Indication:	Pediatric Exclusivity (≥ 3 years old)
Dosage Form and Route of Administration:	Ophthalmic solution for topical ocular administration

Acular (ketorolac tromethamine ophthalmic solution 0.5%) is a topical nonsteroidal anti-inflammatory drug (NSAID) indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis and for post-surgical inflammation following cataract surgery. Acular PF is the preservative free formulation of ketorolac tromethamine ophthalmic solution 0.5% and is indicated for the pain and photophobia following incisional refractive surgery. Ketorolac's most common adverse events include transient burning and stinging upon instillation. These events are reported by up to 40% of subjects using ketorolac and up to 20% of subjects using the preservative free formulation. A written request for the use of Acular in the pediatric population was sent to the sponsor on May 10, 2000 to evaluate the safety and tolerability in this population. It was the agency's view that efficacy data could be reliably extrapolated from the existing clinical database. It was also determined by the agency that safety data gathered from evaluating the preserved from of this product would yield adequate information that could

be applied to the non-preserved formulation. Therefore, this submission contains clinical data which assesses the safety and tolerability of Acular (ketorolac tromethamine ophthalmic solution 0.5%) only.

II. Clinically Relevant Findings from Chemistry,Toxicoloy,Microbiology,Biopharmaceutics, Statistics and/or Other Consultant Reviews - N/A

III. Human Pharmacokinetics and Pharmacodynamics - N/A

IV. Description of Clinical Data Sources

Table 1 – Clinical Data Sources

Protocol Type	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	Sex/Race	No. Patients Enrolled/ Completed
Phase IV Studies							
Safety 190442-004	Multi-center, randomized, double-masked, vehicle-controlled	6 weeks	Normal pediatric patients	Ketorolac tromethamine 0.5% Vehicle of ketorolac tromethamine 0.5%	QID QID	**sex** M: 54% (68/126) F: 46% (58/126) **race** C: 91.3% (115/126) B: 2.4% (3/126) H: 6.3% (8/126)	126 enrolled 120 complete

V. Clinical Review Methods

The overall approach to the review of this supplement was to determine the safety profile of Acular in the pediatric population. The adverse event rates as well as tolerability scores were used in the overall evaluation.

VI. Integrated Review of Efficacy – N/A

VII. Integrated Review of Safety

A. Conclusions:

There were no differences between subjects receiving Ketorolac, and subjects receiving vehicle, in any of the measured safety parameters including adverse events, subject tolerability to treatment, visual acuity measurements and biomicroscopy findings, during the course of the study. Ketorolac has an acceptable safety profile for use in a pediatric population ≥3 years of age with a one drop per eye, q.i.d dosing regimen.

B. Individual Study Review

Study 1

Protocol CTN: 9400PG034

Title: A Multi-Center, Randomized, Double-Masked, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Tolerability of Ketorolac Tromethamine 0.5% Ophthalmic Solution Used Four Times Daily for 6 Weeks in Normal Pediatric Subjects.

Objective: To evaluate the safety and tolerability of ketorolac tromethamine 0.5% ophthalmic solution in normal pediatric subjects.

Study Design

This was a multi-center, randomized, double-masked, vehicle-controlled, parallel-group study with 4 scheduled visits over a period of 6 weeks. Approximately 120 subjects were to be enrolled at approximately five sites to achieve the desired sample size of at least 90 completed subjects, approximately evenly distributed among one-year age groups. Qualified subjects were assigned to one of two treatment groups at Visit 1 (Day 0). Based upon a 2:1 (ketorolac tromethamine 0.5% ophthalmic solution:vehicle of ketorolac

tromethamine 0.5% ophthalmic solution) randomization scheme for QID dosing over a period of approximately 42 days.

Test Drug Schedule: One drop administered in each study eye daily.

Study Population – Inclusion and Exclusion Criteria

Inclusion Criteria

The following were requirements for entry into the study:

1. Age 3 (i.e., have had their third birthday) to 12 years (i.e., have not had their 13th birthday), by Visit I (baseline)
2. Normal ocular examination including corrected (if necessary) visual acuity of 20/63 or better in each eye
3. Completed Informed Consent Form by the subject and subject's parent/legally-authorized representative(s) (or as otherwise required) and completed Subject Assent Form from subjects ≥7 years of age (or as otherwise required).

Exclusion Criteria

The following were criteria for exclusion from participating in this study:

1. Active ocular disorder (excluding refractive disorders)
2. History of ocular surgery
3. Prior (within 5 days of beginning study treatment) use of any ophthalmic agents
4. Prior (within 5 days of beginning study treatment) use of any contact lenses
5. Prior (within 2 weeks of beginning study treatment) use of non-steroidal anti-inflammatory medications (e.g., aspirin, ibuprofen, naproxen, diclofenac), corticosteroids, or anti-coagulants
6. Prior (within 7 days of beginning study treatment) active illness (e.g. upper respiratory tract infection)
7. Body weight below 5th percentile for age
8. Sensitivity or poor tolerance to any component of the study treatments or any non-steroidal anti-inflammatory medications
9. Prior (within 45 days of beginning study treatment) use of an investigational drug or device

10. Child-bearing potential
11. Any acute or chronic medical condition, including, but not limited to, hematological disorders or history of excessive bleeding (e.g., nosebleeds)
12. Subject has a condition or is in a situation which, in the Investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study

Study Medications

Ketorolac (AGN8344X) contains 0.5% ketorolac tromethamine (5mg/ml), benzalkonium chloride 0.01 %, edetate disodium 0.1 %, octoxynol 40, sodium chloride, hydrochloric acid and/or sodium hydroxide to adjust pH to 7.2- 7.4, and purified water.

Vehicle (AGN8460X) contains benzalkonium chloride 0.01%, edetate disodium 0.1%, octoxynol 40, sodium chloride, hydrochloric acid and/or sodium hydroxide to adjust pH to 7.2- 7.4, and purified water.

Efficacy Variable
Not applicable.

Safety Variable

Adverse Events
Throughout the course of the study, all adverse events were monitored. All subject reported and/or investigator observed adverse events were documented on the appropriate CRF , along with information which included the onset date, resolution date (if applicable), duration, severity, whether or not the event was serious, relationship to study drug (in all instances, derived from the investigators), whether treatment was required, and the outcome of the event.

Visual Acuity
The best-corrected visual acuity (VA) was measured for each eye using a standard ETDRS chart at the baseline visit and at each follow-up visit. In the event that a child could not yet identify letters on the ETDRS chart, a standard LEA symbols chart was used to measure the VA, following the same guidelines used with the ETDRS chart.

Biomicroscopy
Slit lamp biomicroscopy (without pupil dilation) was measured at the baseline visit and at each follow-up visit. Evaluations included the lid and lid margin for erythema and swelling; the conjunctiva (palpebral and bulbar) for erythema and chemosis; the cornea for edema and erosion; the endothelium, lens pathology for cataracts; and the anterior chamber for cells and flare.

Physical Examination

Each subject was to undergo a physical examination, conducted at visit 1 (baseline) by a board-certified pediatrician, in the presence of the parent/legal guardian.

Tolerability Assessment

The investigator and designated site personnel were to ask the subject's parent/legal guardian to rate their child's overall comfort using the following 5-point scale: Intolerable, Very Uncomfortable, Moderately Uncomfortable, Slightly Uncomfortable, Comfortable.

Table 2 – Examination Schedule

	Visit 1 (Baseline) Day 0	Visit 2 (Week 1) Day 7	Visit 3 (Week 3) Day 21	Visit 4 (Week 6) Day 42
Physical Exam	X			
Visual Acuity	X	X	X	X
Biomicroscopy	X	X	X	X
Tolerability Assessment		X	X	X
Assessment of Adverse Events	X	X	X	X

Subject Disposition and Demographics

There were 126 subjects enrolled in this study: 83 subjects randomized to Ketorolac QID, and 43 subjects randomized to Vehicle QID. 95.2% of subjects completed the study; 94% (78/83) in the Ketorolac group, and 97.7% (42/43) in the Vehicle group.

Table 3 - Demographic Data

		Ketorolac (n=83)	Vehicle (n=43)	Total (n=126)	P - Value
Age (years)	Mean	7.4	7	7.3	0.456
	SD	2.87	2.76	2.83	
	Median	7	7	7	
	Min	3	3	3	
	Max	12	12	12	
Sex	Male	47 (56.6%)	21 (48.8%)	68 (54%)	0.520
	Female	36 (43.4%)	22 (51.2%)	58 (46%)	
Race	Caucasion	79 (95.2%)	36 (83.7%)	115 (91.3%)	0.045 (a)
	Black	2 (2.4%)	1 (2.3%)	3 (2.4%)	
	Hispanic	2 (2.4%)	6 (14%)	8 (6.3%)	
Iris color	Blue	41 (49.4%)	21 (48.8%)	62 (49.2%)	0.363 (b)
	Brown	25 (30.1%)	17 (39.5%)	42 (33.3%)	
	Green	4 (4.8%)	2 (4.7%)	6 (4.8%)	
	Hazel	13 (15.7%)	3 (7%)	16 (12.7%)	

(a) comparison of caucasion vs. non-caucasion

(b) comparison of blue vs. brown vs. (green or hazel)

Table 4 - Age Distribution

	Ketorolac (n=83)	Vehicle (n=43)	Total (n=126)
Age (years)			
3	9 (10.8%)	6 (14%)	15 (11.9%)
4	6 (7.2%)	4 (9.3%)	10 (7.9%)
5	10 (12%)	5 (11.6%)	15 (11.9%)
6	11 (13.3%)	3 (7%)	14 (11.1%)
7	7 (8.4%)	6 (14%)	13 (10.3%)
8	8 (9.6%)	5 (11.6%)	13 (10.3%)
9	8 (9.6%)	5 (11.6%)	13 (10.3%)
10	8 (9.6%)	3 (7%)	11 (8.7%)
11	8 (9.6%)	4 (9.3%)	12 (9.5%)
12	8 (9.6%)	2 (4.7%)	10 (7.9%)

Table 5 – Discontinued Patients and Reason

Patient Number	Treatment	Age	Reason
1059	vehicle	5	Exclusion criteria – chronic medical condition (neurofibromatosis)
1144	ketorolac	9	Exclusion criteria – chronic medical condition (cerebral palsey)
1088	ketorolac	7	Exclusion criteria – chronic medical condition (cerebral palsey)
1003	ketorolac	3	Parent/legal guardian choice
1005	ketorolac	3	Parent/legal guardian choice
1004	vehicle	3	Parent/legal guardian choice

Results – Protocol 190442-004

Adverse Events

All 126 subjects who enrolled in the study received at least one dose of study medication and were included in the safety analysis. 34.9% (29/83) of subjects in the

Ketorolac treatment group and 32.6% (14/43) of subjects in the Vehicle treatment group experienced one or more adverse events. The most common ocular adverse events were stinging of the eye (9.6%), and burning eyes (3.6%) in the Ketorolac treatment group, and stinging of the eye (9.3%) in the Vehicle treatment group., There were no differences in Adverse Event reports between the Ketorolac and Vehicle groups across all age groups.

There were no deaths or serious adverse events reported during the course of the study. There were no subjects who discontinued due to an adverse event. There was one unexpected non-serious adverse event that was reported at study center/investigator 3520. This was an ocular adverse event (follicular conjunctivitis) that was considered to be possibly related to the study drug, and the information was forwarded appropriately to the governing IRB.

Table 6 - Number (%) of Subjects with Adverse Events, Reported by at Least 2% of Subjects in Either Treatment Group

Body System Preferred Terms	Ketorolac N = 83	Vehicle N = 43
Body as a whole		
Infection	6 (7.2)	3 (7.0)
Fever	2 (2.4)	2 (4.7)
Injury Accident	2 (2.4)	0
Malaise	0	1 (2.3)
Body / Head		
Headache	4 (4.8)	0
Respiratory / General		
Cough Increase	3 (3.6)	1 (2.3)
Respiratory / Nose		
Rhinitis	0	3 (7.0)
.Pharyngitis	0	1 (2.3)
Respiratory / NASP		
Pharyngitis	3 (3.6)	0
Special Senses / Ocular		
Stinging	8 (9.6)	4 (9.3)
Burning	3 (3.6)	0
Irritation	2 (2.4)	1 (2.3)
Pruritis	0	1 (2.3)
Conjunctivitis (NOS)	1 (1.2)	1 (2.3)
Viral Conjunctivitis	0	1 (2.3)
Conjunctival Hyperemia (NOS)	0	1 (2.3)
Epiphora	0	1 (2.3)
Corneal Scar	0	1 (2.3)

Reviewer's Comments:
It is expected that the actual adverse event rate of burning and stinging seen in practice will be higher than that seen in these healthy volunteers. It may be closer to the 40 % seen in the adult population.

Visual Acuity

Subject's visual acuity was compared to baseline (visit 1 -day 0) acuity based upon worse eye, at each of the three follow-up visits in the study. Approximately 99% of subjects in the Ketorolac treatment group had no clinically significant change in visual acuity. Three subjects (#s1074, 1098, and 1190) had a three line decrease in visual acuity over the course of the study in one eye only. All three returned to normal vision. Further investigation revealed that they did not have best corrected visual acuity measured at these visits. All of the subjects in the Vehicle group had no significant change in visual acuity during the study.

Table 7 – Change in Visual Acuity

Day	Change in Vision	Ketorolac	Vehicle	P-value
7	Yes (a) No (b)	1 (1.2%) 82 (98.8%)	0 43 (100%)	1.00
21	Yes (a) No (b)	2 (2.5%) 77 (97.5%)	0 42 (100%)	0.543
42	Yes (a) No (b)	1 (1.3%) 77 (98.7%)	0 42 (100%)	1.00

(a) 3 or more line decrease in eye with worse change
(b) less than 3 line decrease, no change, or increase in visual acuity in eye with worse vision

Biomicroscopy

Table 8 - Mean Biomicroscopy Scores (All eyes)

		Day 0	Day 7	Day 21	Day 42
Lid erythema	Ketorolac	0.02	0.02	0.03	0.01
	vehicle	0.02	0.02	0.01	0
Lid swelling	Ketorolac	0	0.04	0.01	0
	vehicle	0	0.05	0.04	0
Conjunctival hyperemia	Ketorolac	0.19	0.2	0.09	0.11
	vehicle	0.10	0.16	0.13	0.10
Chemosis	Ketorolac	0.10	0.10	0.03	0.06
	vehicle	0.06	0.06	0.02	0.03
Corneal Edema	Ketorolac	0	0	0	0
	vehicle	0	0	0	0
Corneal Erosion	Ketorolac	0.03	0.02	0.05	0.04
	vehicle	0.06	0	0	0.04
Cell	Ketorolac	0	0	0	0
	vehicle	0	0	0	0
Flare	Ketorolac	0	0	0	0
	vehicle	0	0	0	0
Lens Pathology	Ketorolac	0	0	0	0
	vehicle	0	0	0	0

Note: Assesement scale = (0/0.5/1.0/1.5/2.0/2.5/3.0/3.5/4.0)
0=none, 1.0=mild, 2.0=moderate, 3.0=severe, 4.0=very severe

Reviewer's Comments:
Mean biomicroscopy scores did not reach clinical significance for any of the measured parameters in the ketorolac or vehicle group. There is no statistical or clinical difference in mean biomicroscopy scores between groups.

Tolerability Assessment

Subject tolerability was assessed at each of the three follow-up visits. Tolerability was graded by the parent/legal guardian of each subject, and was recorded on a 5-point scale. There were no statistically significant differences in tolerability between the Ketorolac treated group and the Vehicle treated group at each follow-up visit ($p \geq 0.299$).

Table 9 – Tolerability Rating

	Ketorolac	Vehicle	p-value
Day 7			
N	83	43	0.819 (a)
Comfortable	62 (74.7%)	33 (76.7%)	
Slightly uncomfortable	19 (22.9%)	9 (20.9%)	
Moderately uncomfortable	2 (2.4%)	1 (2.3%)	
Very uncomfortable	0	0	
Intolerable	0	0	
Day 21			
N	79	42	0.824 (a)
Comfortable	61 (77.2%)	33 (78.6%)	
Slightly uncomfortable	17 (21.5%)	8 (19.0%)	
Moderately uncomfortable	1 (1.3%)	0	
Very uncomfortable	0	1 (2.4%)	
Intolerable	0	0	
Day 42			
N	78	42	0.299 (a)
Comfortable	63 (80.8%)	35 (83.3%)	
Slightly uncomfortable	15 (19.2%)	4 (9.5%)	
Moderately uncomfortable	0	1 (2.4%)	
Very uncomfortable	0	1 (2.4%)	
Intolerable	0	1 (2.4%)	

(a) p-value based on the Pearson chi-square test for trend

VIII. **Dosing, Regiment, and Administration Issues - N/A**

IX. **Use in Special Populations - N/A**

X. **Labeling**

Reviewer's Comments:
Recommended additions are shown by underlining and recommended deletions are shown by strikethrough lines.

10 Page(s) Withheld

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BH ✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1a

U.S. Patent Nos.: 4,454,151; 5,110,493; and 5,414,011.

Revised August 2001

XI. Conclusions and Recommendations

A. Conclusions

The sbumitted study demonstrates the safety and tolerability of ketorolac tromethamine ophthalmic solution for use in a pediatric population ≥3 years of age with a one drop per eye, q.i.d dosing regimen.

B. Recommendation:

Supplemental NDA 19-700/S-019 and NDA 20-811/S-003 is recommended for approval for use in the pediatric population ≥ 3years of age with the revised labeling identified in this review.

Jennifer D. Harris, M.D.
Medical Officer, Ophthalmology

cc:
Original NDA 19-700 & 20-811
HFD-550/Div Files
HFD-550/MO/Harris
HFD-550/Chem/Tso
HFD-550/PM/Puglisi
HFD-550/Pharm/ZChen
HFD-550/Stat/Lin
HFD-550/PK/Bashaw
HFD-340/Carreras
HFD-550/SMO/Chambers
HFD-550/Acting Div Dir/Bull

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Jennifer Harris
9/5/01 07:30:35 AM
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Wiley Chambers
9/6/01 09:26:37 AM
MEDICAL OFFICER

Medical Officer's Review
Supplemental NDA 19-700/S-019
&
Supplemental NDA 20-811/S-003

NDA 19-700 & 20-811	Submission: 10/2/01
Medical Officer's Review # 2	Review Completed: 10/15/01

Proposed Tradename: Acular (ketorolac tromethamine 0.5%)
Acular PF (ketorolac tromethamine 0.5%)

Sponsor: Allergan
2525 Dupont Drive
P.O. Box 19534
Irvine, California 92623
Attn: Elizabeth Bancroft

Pharmacologic Category: Non-steroidal anti-inflammatory

Proposed Indication: Pediatric Exclusivity (≥ 3 years old)

Submitted: Revised labeling submitted by the company

12 Page(s) Withheld

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B4 ✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 2a

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Jennifer Harris
11/2/01 01:41:27 PM
MEDICAL OFFICER

Wiley Chambers
11/23/01 10:11:11 PM
MEDICAL OFFICER

Medical Officer's Review
Supplemental NDA 19-700/S-019
&
Supplemental NDA 20-811/S-003

NDA 19-700 & 20-811	Submission:	12/6/01 (via email) 1/17/02 (official)
Medical Officer's Review # 3	Review Completed:	12/17/01

Proposed Tradename: Acular (ketorolac tromethamine 0.5%)
Acular PF (ketorolac tromethamine 0.5%)

Sponsor: Allergan
2525 Dupont Drive
P.O. Box 19534
Irvine, California 92623
Attn: Elizabeth Bancroft

Pharmacologic Category: Non-steroidal anti-inflammatory

Proposed Indication: Pediatric Exclusivity (≥ 3 years old)

Submitted: Revised labeling submitted by the company

11 Page(s) Withheld

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Withheld Track Number: Medical- 3a

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1/25/02 01:39:52 PM
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Wiley Chambers
1/30/02 10:23:37 AM
MEDICAL OFFICER

Medical Officer's Review
Supplemental NDA 19-700/S-019
&
Supplemental NDA 20-811/S-003

NDA 19-700 & 20-811	Submission: 1/22/02
Medical Officer's Review # 4	Review Completed: 1/25/02

Proposed Tradename:	Acular (ketorolac tromethamine 0.5%) Acular PF (ketorolac tromethamine 0.5%)
Sponsor:	Allergan 2525 Dupont Drive P.O. Box 19534 Irvine, California 92623 Attn: Elizabeth Bancroft
Pharmacologic Category:	Non-steroidal anti-inflammatory
Proposed Indication:	Pediatric Exclusivity (≥ 3 years old)
Submitted:	Revised labeling submitted by the company

10 Page(s) Withheld

_____ Trade Secret / Confidential

B4 ✓ Draft Labeling

_____ Deliberative Process

With

Store ACULAR® PF between 15°C - 30°C (59°F - 86°F) with protection from light.
Rx only

U.S. Patent Nos.: 4,454,151; 5,110,493; and 5,414,011.

ACULAR® is a registered trademark of SYNTEX (U.S.A.) Inc. ACULAR® PF is manufactured and distributed by ALLERGAN under license from its developer, SYNTEX (U.S.A.) Inc., Palo Alto, California, U.S.A.

Revised January 2002
8718X

Conclusions/Recommendations

The enclosed labeling is acceptable. Following resolution of any chemistry/manufacturing issues, Supplemental NDA 19-700/S-019 and Supplemental NDA 20-811/S-003 are recommended for approval.

Jennifer D. Harris, MD
Medical Officer, Ophthalmology

Orig. NDA 19-700 & 20-811
HFD-550/Div Files
HFD-550/MO/Harris
HFD-550/SMO/Chambers
HFD-550/Div Dir/Simon
HFD-550/Biopharm/Bashaw
HFD-550/Chem/Tso
HFD-550/PharmTox/ZChen
HFD-550/PM/Rodriguez

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-700 / S-019
20-811 / S-003

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW	1. ORGANIZATION HFD-550	2. NDA NUMBER 19-700
3. NAME AND ADDRESS OF APPLICANT *(City and State)* 2525 Dupont Drive P.O.Box 19534 Irvine, CA 92623-9534		4. AF NUMBER 5. SUPPLEMENT(S) *SE5-019 6/18/01 *Original supplement
6. NAME OF DRUG: Acular®(Ketorolac tromethamine ophthalmic solution), 0.5%	7. NONPROPRIETARY NAME Ketorolac tromethamine	
8. SUPPLEMENT PROVIDES FOR: Pediatric exclusivity. Efficacy supplement		9. AMENDMENT(S), REPORT(S), ETC. NUMBER(S) DATE(S) **SE5-019 BC 7/26/01 ** Subject of this review
10. PHARMACOLOGICAL CATEGORY Treatment of seasonal allergic conjunctivitis and for the treatment of postoperative inflammation in patients who have undergone cataract extraction	11. HOW DISPENSED RX X OTC __	12. RELATED IND/NDA/DMF NDA 20-811/SE5-003 6/18/01
13. DOSAGE FORM(S) Ophthalmic solution	14. POTENCY 0.5%	
15. CHEMICAL NAME AND STRUCTURE		16. RECORDS AND REPORTS CURRENT YES __ NO __ REVIEWED YES __ NO __

17. COMMENTS:

a. The original supplement NDA 19-700/SE5-019 (pediatric exclusivity clinical supplement) was submitted on 6/18/01.
b. Reference is made to the Agency's telecon dated 7/18/2001 requesting an environmental assessment for the above supplement, S-019.
c. Allergan in amendment dated 7/26/2001 (**the subject of this review**) have requested for a categorical exclusion from the environmental assessment in accordance with 21 CFR 25.31(b).

18. CONCLUSIONS AND RECOMMENDATIONS:

From CMC viewpoint, this supplement is approved.

cc:
Orig. NDA 19-700/SE5-019
HFD-550/div. File
HFD-550/HKhorshidi
HFD-550/LNg
HFD-550/WChambers
HFD-550/RRodriguez
HFD-830/CW Chen

R/D Init. by:__LNg
F/T by: HKhorshidi
doc # N:\NDA\19-700\SE5-019\Chem\2001-08.07. REV

19. REVIEWER NAME: Hossein S. Khorshidi	SIGNATURE	DATE COMPLETED

Review Note

1. The original supplement S-019 (pediatric exclusivity clinical supplement) was submitted on 6/18/2001.

2. Reference is made to the Agency's telecon dated 7/18/2001 requesting an environmental assessment for the above supplement, S-019.

3. Allergan in amendment dated 7/26/2001 (**the subject of this review**) have attached a claim for a categorical exclusion from the requirement to prepare an environmental assessment for Acular®(Ketorolac tromethamine ophthalmic solution), 0.5% in accordance with 21 CFR 25.31(b).

4. According to the applicant, the approval of supplement S-019 would increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below *1 part per billion* which would not affect the human environment as a result of the proposed action.

Note:

It should be mentioned that the drug substance and the drug product are exactly the same as approved NDA #19-700 and no changes have been implemented in manufacturing/or processing for this product.

Evaluation:

Since no major CMC issues are concerned with supplement S-019, therefore, and from CMC standpoint, it is approved.

Satisfactory

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/s/

Hossein Khorshidih
8/14/01 12:22:59 PM
CHEMIST

Linda Ng
8/17/01 10:30:23 AM
CHEMIST

CHEMIST'S REVIEW	1. ORGANIZATION HFD-550	2. NDA NUMBER 20-811
3. NAME AND ADDRESS OF APPLICANT *(City and State)* 2525 Dupont Drive P.O.Box 19534 Irvine, CA 92623-9534		4. AF NUMBER 5. SUPPLEMENT(S) *SE5-003 6/18/01 *Original supplement
6. NAME OF DRUG: Acular®PF (Ketorolac tromethamine ophthalmic solution), 0.5% preservative-Free	7. NONPROPRIETARY NAME Ketorolac tromethamine	
8. SUPPLEMENT PROVIDES FOR: Pediatric exclusivity supplement. Efficacy supplement		9. AMENDMENT(S), REPORT(S), ETC. NUMBER(S) DATE(S) **20-811/SE5-003 BC 7/26/01 ** Subject of this review
10. PHARMACOLOGICAL CATEGORY For the reduction of ocular pain and photophobia following incisional refractive surgery	11. HOW DISPENSED RX X OTC __	12. RELATED IND/NDA/DMF NDA 19-700/SE5-019 6/18/01
13. DOSAGE FORM(S) Ophthalmic solution	14. POTENCY 0.5%	
15. CHEMICAL NAME AND STRUCTURE		16. RECORDS AND REPORTS CURRENT YES__NO__ REVIEWED YES__NO__

17. COMMENTS:

a. The original supplement NDA 20-811/SE5-003 (pediatric exclusivity clinical supplement) was submitted on 6/18/01.
b. Reference is made to the Agency's telecon dated 7/18/2001 requesting an environmental assessment for the above supplement, S-003.
c. Allergan in amendment dated 7/26/2001 (**the subject of this review**) have requested for a categorical exclusion from the environmental assessment in accordance with 21 CFR 25.31(b).

18. CONCLUSIONS AND RECOMMENDATIONS:
From CMC viewpoint, this supplement is approved.

cc:
Orig. NDA 20-811/SE5-003
HFD-550/div. File
HFD-550/HKhorshidi
HFD-550/LNg
HFD-550/WChambers
HFD-550/RRodriguez
HFD-830/CW Chen

R/D Init. by:__LNg
F/T by: HKhorshidi
doc # N:\NDA\20-811\SE5-003\Chem\2001-08.07. REV

19. REVIEWER NAME: Hossein S. Khorshidi	SIGNATURE	DATE COMPLETED

Review Note

1. The original supplement 20-811/S-003 (pediatric exclusivity clinical supplement) was submitted on 6/18/2001.

2. Reference is made to the Agency's telecon dated 7/18/2001 requesting an environmental assessment for the above supplement, S-003.

3. Allergan in amendment dated 7/26/2001 (**the subject of this review**) have attached a claim for a categorical exclusion from the requirement to prepare an environmental assessment for Acular®PF (Ketorolac tromethamine ophthalmic solution), 0.5% in accordance with 21 CFR 25.31(b).

4. According to the applicant, the approval of supplement S-003 would increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below *1 part per billion* which would not affect the human environment as a result of the proposed action.

Note:

It should be mentioned that the drug substance and the drug product are exactly the same as approved NDA #20-811 and no changes have been implemented in manufacturing/or processing for this product.

Evaluation:

Since no major CMC issues are concerned with supplement S-003, therefore, and from CMC standpoint, it is approved.

Satisfactory

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/s/

Hossein Khorshidih
8/14/01 12:25:25 PM
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Linda Ng
8/17/01 10:26:49 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-700 / S-019
20-811 / S-003

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PATENT INFORMATION

The following patents are currently in effect for ACULAR® (ketorolac tromethamine ophthalmic solution) 0.5%.

Patent Numbers:	4,454,151 / 5,110,493
Expiration Dates:	March 22, 2002 / May 5, 2009
Type of Patents:	Drug (Use, Composition / Formulation)
Patent Owner:	SYNTEX (U.S.A.) LLC.

PATENT CERTIFICATION

I, the undersigned, hereby declare that U.S. Patent Nos. 4,454,151 and 5,110,493 cover the use/composition and formulation of ACULAR® (ketorolac tromethamine ophthalmic solution) 0.5%, the product for which approval is being sought for this pediatric supplement and subsequent six month patent extension. Allergan, Inc. has exclusive rights to both of these patents by agreement with the patents' owner, Syntex (U.S.A.) LLC., a Delaware corporation.

ALLERGAN, INC.

By: _____ MAY 22, 2001
Martin A. Voet
Vice President, Chief Intellectual Property Counsel
and Assistant Secretary

Date

Allergan *Confidential*
ACULAR ophthalmic solution

NDA 19-700
NDA 20-811

PATENT CERTIFICATION

I, the undersigned, hereby declare that Patent No. 4,454,151 covers the use/composition of ACULAR® PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free, the product for which approval is being sought for this pediatric supplement and subsequent six month patent extension. Allergan, Inc. has exclusive rights to this patent by agreement with the patent owner, Syntex (U.S.A.) LLC., a Delaware corporation.

ALLERGAN, INC.

By: _____ 10/17/01
Martin A. Voet Date
Vice President, Chief Intellectual Property
Counsel and Assistant Secretary

EXCLUSIVITY SUMMARY for NDA # 19700 SUPPL # 019

Trade Name Acular Generic Name ketorolac tromethamine 0.5%

Applicant Name Allergan HFD- 550

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE5

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO /_X__/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /_X__/NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Applicant only requested pediatric exclusivity

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_X__/ NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-700 Ketorolac Tromethamine 0.5%

NDA # 20-811 Ketorolac Tromethamine 0.5%

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 190442-004

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # 190442-004

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 21,132 YES /_X__/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

Signature of Preparer
Title: medical officer

2/1/02
Date

_____
Signature of Office or Division Director

_____
Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

EXCLUSIVITY SUMMARY for NDA # 20-811 SUPPL # 003

Trade Name Acular PF Generic Name ketorolac tromethamine 0.5%

Applicant Name Allergan HFD- 550

Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

   If yes, what type(SE1, SE2, etc.)? SE5

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /___/ NO /_X__/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_X__/NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Applicant only requested pediatric exclusivity

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_X__/ NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-700 Ketorolac Tromethamine 0.5%

NDA # 20-811 Ketorolac Tromethamine 0.5%

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 190442-004

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # _190442-004_____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 21,132 YES /_X__/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

_____ 2/1/02

Signature of Preparer Date

Title: medical officer

_____ _____

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA **5/10/00**. Application Written Request was made to: NDA# **19-700 & 20-811**
Timeframe Noted in Written Request for Submission of Studies **12/31/01**.
NDA# **19-700 & 20-811** Supplement # **003** Choose one: SE1 SE2 SE3 SE4 **SE5** SE6 SE7 SE8 SLR
Sponsor **Allergan, Inc**
Generic Name **ketorolac tromethamine** Trade Name **Acular and Acular PF**
Strength **0.5%** Dosage Form/Route **topical ophthalmic solution**
Date of Submission of Reports of Studies **6/18/01**.
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) **9/17/01**.

Was a formal Written Request made for the pediatric studies submitted?	Y √	N
Were the studies submitted after the Written Request?	Y √	N
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y √	N
Was the timeframe noted in the Written Request for submission of studies met?	Y √	N
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y √	N
Did the studies fairly respond to the Written Request?	Y √	N

FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-002.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity **√ Granted** **___ Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
20-811	4454151	Mar 22, 2002
19-700	5110493	May 5, 2009

SIGNED {See appended electronic signature page}

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Steven Galson
9/7/01 10:21:18 AM

ALLERGAN, INC.

DEBARMENT CERTIFICATION

Reference: NDA 19-700
ACULAR® (ketorolac tromethamine ophthalmic solution) 0.5%

Under the provisions of Section 306(k) of the Federal Food, Drug and Cosmetic Act, Allergan has made a diligent effort to insure that no individual, corporation, partnership or association debarred under Section 306(a) or 306(b) of the Act, as referenced above, has provided any services in connection with this supplemental application.

Allergan, Inc. further certifies that it did not and will not use in any capacity, the services of any individual, corporation, partnership or association debarred under Section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this supplement.

Peter J. Kresel

Peter Kresel
Senior Vice President
Global Regulatory Affairs
Allergan

5/14/01
Date

ALLERGAN, INC.

DEBARMENT CERTIFICATION

Reference: NDA 20-811
ACULAR® PF (ketorolac tromethamine ophthalmic solution) 0.5%
Preservative-Free

Under the provisions of Section 306(k) of the Federal Food, Drug and Cosmetic Act, Allergan has made a diligent effort to insure that no individual, corporation, partnership or association debarred under Section 306(a) or 306(b) of the Act, as referenced above, has provided any services in connection with this supplemental application.

Allergan, Inc. further certifies that it did not and will not use in any capacity, the services of any individual, corporation, partnership or association debarred under Section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this supplement.

E Bannister for P Kresel
Peter Kresel
Senior Vice President
Global Regulatory Affairs
Allergan

10/17/01
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	List Attached	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Eric Brandt	Corporate Vice President and Chief Financial Officer
FIRM/ORGANIZATION: Allergan, Inc.	
SIGNATURE	DATE: 5/18/01

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by Electronic Document Services/USDHHS: (301) 443-2454 EF

LIST OF PRINCIPAL INVESTIGATORS/SUBINVESTIGATORS

Inv. ID No.	Principal Investigator	Subinvestigators	Address	Phone/Fax

NDA SUPPL AMENDMENT
SES-019/BL

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

January 17, 2002

RECEIVED
JAN 22 2002
MEGA/CDER

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: NDA 19-700 / ACULAR® (ketorolac tromethamine ophthalmic solution) 0.5%, **Amendment to Supplement S-019 / Revised Draft Package Insert** and NDA 20-811 / ACULAR®PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free, **Amendment to Supplement S-003 / Revised Draft Package Insert**

Dear Dr. Chambers:

Reference is made to my December 6, 2001 E-mail sent to Raphael Rodriguez, Project Manager, which contained revised versions of the ACULAR® and ACULAR®PF annotated draft package inserts. These draft package inserts were originally included in Supplements S-019 and S-003, the pediatric exclusivity clinical supplements submitted to the Agency on June 18, 2001.

At this time we are submitting the official copy of both revised draft package inserts to their respective NDA's. Section 1 contains the revised draft package insert for ACULAR® and Section 2 contains the revised draft package insert for ACULAR®PF.

The final versions of both draft package inserts as agreed upon by the Agency and Allergan in our January 7, 2002 teleconference will be submitted to the Agency by the end of the month.

We trust that the enclosed information is satisfactory and request that it be included in the files for NDA 19-700 and NDA 20-811. Should you have any questions, please contact me by telephone (714) 246-4391 or fax (714) 246-4272, or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

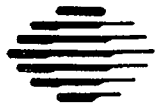
Elizabeth Bancroft

Elizabeth Bancroft
Senior Director
Regulatory Affairs

DUPLICATE

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com



January 22, 2002

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: NDA 19-700 / ACULAR® (ketorolac tromethamine ophthalmic solution) 0.5%, **Amendment to Supplement S-019 / Final Revised Draft Package Insert** and NDA 20-811 / ACULAR®PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free, **Amendment to Supplement S-003 / Final Revised Draft Package Insert**

Dear Dr. Chambers:

Reference is made to our January 7, 2002 teleconference in which we discussed the Agency's additional revisions for the ACULAR® and ACULAR®PF draft package inserts. These draft package inserts were originally included in the pediatric exclusivity clinical supplements submitted to the Agency on June 18, 2001.

At this time we are submitting the final versions of both package inserts to the Agency with the agreed upon changes. The following revisions have been made to both draft package inserts:

1. Under Description, 1st paragraph, 2nd sentence: the chemical name has been revised to be consistent with the USAN.

2. Under Precautions, 3rd paragraph, 1st sentence: added "complicated ocular surgeries,".

3. Under Precautions, inserted a new 4th paragraph which reads "Postmarketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events."

4. Under Adverse Reactions, 4th paragraph, last sentence: alphabetized the four events in the last sentence to read "include corneal erosion, corneal perforation, corneal thinning and epithelial breakdown".

Appended in Section 1 is the final revised draft package insert for ACULAR® ophthalmic solution. Section 2 contains the final revised draft package insert for ACULAR®PF ophthalmic solution.

We trust that the enclosed information is satisfactory for your review and approval and request that it be included in the files for NDA 19-700 and NDA 20-811. Should you have any questions, please contact me by telephone (714) 246-4391 or fax (714) 246-4272, or e-mail at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs

SE5-019 BL

NDA SUPPL AMENDMENT

LLERGAN

Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

October 2, 2001

RECEIVED

OCT 0 3 2001

MEGA/CDER

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: NDA 19-700 / ACULAR® (ketorolac tromethamine ophthalmic solution) 0.5%, **Amendment to Supplement S-019 / Revised Draft Package Insert** and NDA 20-811 / ACULAR®PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free, **Amendment to Supplement S-003 / Revised Draft Package Insert**

Dear Dr. Chambers:

Reference is made to the September 9, 2001 facsimile received from Raphael Rodriguez, Project Manager, containing the Agency recommended revisions to the ACULAR® and ACULAR®PF draft package inserts. These draft package inserts were included in Supplements S-019 and S-003, the pediatric exclusivity clinical supplements submitted to the Agency on June 18, 2001.

In response to the Agency's comments, a revised copy of the annotated draft package insert for ACULAR® (ketorolac tromethamine ophthalmic solution) 0.5% is appended in Section 1 and a revised copy of the annotated draft package insert for ACULAR®PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free is appended in Section 2.

Allergan has discussed the proposed revisions to the Precautions section of the ACULAR® and ACULAR®PF labeling with CibaVision since we understand the Agency is seeking identical, class language for Voltaren. As a result of those discussions we are proposing revised wording that both companies feel adequately addresses the topic of potential effects with NSAIDs consistent with the findings of the ASCRS, which were reported in the April, 2001 issue of the Journal of Cataract and Refractive Surgery. A copy of the article is appended in Section 3.

DUPLICATE

We trust that the enclosed information is satisfactory for your review and approval and request that it be included in the files for NDA 19-700 and NDA 20-811. Should you have any questions, please contact me by telephone (714) 246-4391 or fax (714) 246-4272, or email at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Senior Director
Regulatory Affairs

NDA SUPPL AMENDMENT SES-003/BL

LLERGAN

5 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

August 27, 2001

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: NDA 20-811 / ACULAR®PF (ketorolac tromethamine ophthalmic solution)
0.5% Preservative-Free
Amendment to Supplement S-003 / Draft Package Insert

Dear Dr. Chambers:

Reference is made to the August 24, 2001 telephone call from Raphael Rodriguez, Project Manager, requesting a draft package insert specifically for ACULAR®PF from Allergan for Supplement S-003, the pediatric exclusivity clinical supplement which was submitted to the Agency on June 18, 2001.

In response to the Agency's request, a copy of the draft and annotated draft package insert for ACULAR®PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free is appended in Section 1. An identical copy of this information was sent to Raphael Rodriguez by facsimile on August 24, 2001.

We trust that the enclosed information is satisfactory for your review and request that it be included in the file for NDA 20-811. Should you have any questions, please contact me by telephone (714) 246-4391 or fax (714) 246-4272, or email at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft
Senior Director
Regulatory Affairs

ORIGINAL

LLERGAN

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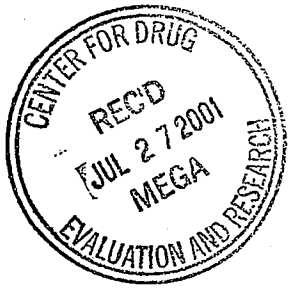
S E S-019 BC

July 26, 2001



Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: NDA 19-700 / ACULAR® (ketorolac tromethamine ophthalmic solution) 0.5%
Amendment to Supplement S-019 / Environmental Assessment

Dear Dr. Chambers:

Reference is made to the July 18, 2001 telephone message received from Raphael Rodriguez, Project Manager, requesting an environmental assessment from Allergan for Supplement S-019, the pediatric exclusivity clinical supplement which was submitted to the Agency on June 18, 2001.

In response to the Agency's request, I have attached a claim for a categorical exclusion from the requirement to prepare an environmental assessment for ACULAR® (ketorolac tromethamine ophthalmic solution) 0.5%.

We trust that the enclosed information is satisfactory for your review and request that it be included in the file for NDA 19-700. Should you have any questions, please contact me by telephone (714) 246-4391 or fax (714) 246-4272, or email at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Senior Director
Regulatory Affairs

ORIGINAL

NDA NO. 19-700 REF. NO. 019
NDA SUPPL FOR SES
SES-019 1PM
NDA SUPPL AMENDMENT

ERGAN

ıont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

June 18, 2001

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Blvd. Building 2
Rockville, MD 20850

Re: NDA 19-700 / ACULAR® (ketorolac tromethamine ophthalmic solution) 0.5%,
NDA 20-811 / ACULAR®PF (ketorolac tromethamine ophthalmic solution) 0.5%
Preservative-Free, **SUBMISSION OF PEDIATRIC STUDY REPORT –
PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**

Dear Dr. Chambers:

Reference is made to the May 10, 2000 Written Request received from the Agency for pediatric information on ketorolac tromethamine ophthalmic solution 0.5% and the October 31, 2000 response by Allergan.

At this time, and in accordance with 21 CFR 201.57 (f)(9), we are submitting an archival and a review copy of a Supplemental Pediatric Study Report to the above-referenced NDAs and requesting that a pediatric exclusivity determination be made.

In support of the proposed new wording to the pediatric use section of the package insert a clinical safety and tolerability study, 190442-004 was conducted. This study was a multi-center, randomized, double-masked, vehicle-controlled, parallel-group study completed in the United States which compared ketorolac solution to its vehicle. A total of 126 patients between the ages of 3 and 12 years were enrolled and 120 patients completed the study.

The results of this study support the hypothesis that ketorolac tromethamine 0.5% ophthalmic solution may be administered in children 3 to 12 years of age four times daily, as currently indicated for an adult population, and that the medication displays an acceptable safety profile, while being well tolerated in a pediatric population.

ORIGINAL

Section 2, Proposed draft labeling and Section 10, SAS Data sets were sent electronically as a Desk Copy to Raphael Rodriguez, Project Manager.

We trust that the enclosed information is satisfactory for your review and approval and request that it be included in the files for NDA 19-700 and NDA 20-811. Should you have any questions, please contact me by telephone (714) 246-4391 or fax (714) 246-4272, or email at bancroft_elizabeth@allergan.com.

Sincerely,

Elizabeth Bancroft

Elizabeth Bancroft
Senior Director
Regulatory Affairs

cc: G. Buehler, Acting Director, OGD