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

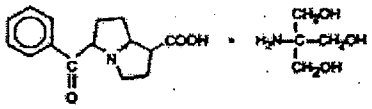
LABELING

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.

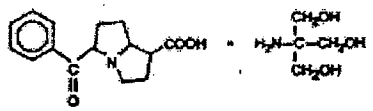
Revised January 2002

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.