CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-528

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: **21-528**
Review number: 000
Sequence number/date/type of submission: 000/August 6, 2002/Commercial
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Allergan Inc., 2525 Dupont Drive, P.O. Box 19534, Irvine 92623-9534
Manufacturer for drug substance: Roche Ireland Limited, Clarecastle, County Clare, Ireland

Reviewer name: Zhou Chen
Division name: Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
HFD #: HFD-550
Review completion date: October 11, 2002

Drug:

Trade name: Unknown
Generic name (list alphabetically): Ketorolac tromethamine ophthalmic solution 0.4%
Code name: Not indicated
Chemical name: 1H-Pyrrolizine-1-carboxylic acid, 5-benzoyl-2,3-dihydro, (±)-, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)
CAS registry number: 74103-07-4
Mole file number: Not indicated
Molecular formula/molecular weight: $C_{19}H_{24}N_2O_6$, MW: 376.41
Structure:

Relevant INDs/NDAs/DMFs: [redacted], NDAs 19-700 and 20-811, [redacted]

Drug class: NSAID

Indication: For the reduction of ocular pain and ocular symptoms of foreign body sensation, burning/stinging, tearing, and photophobia following refractive surgery.

Clinical formulation:

Ingredient	Concentration (% w/v)	Concentration (mg/ml)
Ketorolac tromethamine	0 4	4 0
Benzalkonium chloride, NF	0 006	0 06
Edetate disodium, USP	0 015	0 15
Octoxynol-40	[redacted]	[redacted]
Sodium chloride, USP		
NaOH, NF	pH 7 3-7.5	pH 7 3-7.5
HCl, NF	pH 7 3-7 5	pH 7 3-7 5
Purified water, USP	qs	qs

Route of administration: Topical, Ocular

Proposed use: 1 drop (50 μl) per eye, 4 times daily for up to 4 days (For a 50 kg adult, the total dose can reach 1.6 mg/patient/day or 0.032 mg/kg, 1.18 mg/m^2)

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ON ORIGINAL

Executive Summary

I. Recommendations

A. Recommendation on Approvability

There are no pharmacology/toxicology objections to the approval of this NDA.

B. Recommendation for Nonclinical Studies

No recommendation is necessary.

C. Recommendations on Labeling

Minor modifications of labeling in the "Carcinogenesis, Mutagenesis, Impairment of Fertility" and "Pregnancy" sections are recommended (see Labeling Review).

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

Following topical ocular administration to rabbits, ketorolac tromethamine was rapidly absorbed and well distributed in the eye. The systemic exposure to the drug following ocular administration in rabbits was very low. Topical ocular administration of ketorolac demonstrated potent anti-inflammatory activity in several models of ocular inflammation in rats and rabbits. No biologically significant toxic effects were observed in ocular toxicity studies.

B. Pharmacologic Activity

Ketorolac tromethamine is an NSAID with analgesic, anti-inflammatory, and anti-pyretic activity. The mechanism of the anti-inflammatory and analgesic effects of ketorolac is thought to be, in part, the result of cyclo-oxygenase inhibition and subsequent decreased prostaglandin biosynthesis. Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation.

C. Nonclinical Safety Issues Relevant to Clinical Use

There are no nonclinical safety issues in this NDA relevant to the clinical use of the drug product. Since ketorolac tromethamine ophthalmic solution 0.4% contains lower levels of active and inactive ingredients relative to the currently marketed Acular, the frequency of adverse events is expected to be reduced.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

NDA 21-528/Division File
NDA 21-528/Original NDA
HFD-550/CSO/Rodriguez
HFD-550/MO/Lim
HFD-550/TL Pharm/Yang
HFD-550/Pharm/ChenZ

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PHARMACOLOGY/TOXICOLOGY REVIEW

Reviewer's Comments: Ketorolac tromethamine is an NSAID. Currently marketed topical ophthalmic ketorolac drug products include Acular (for allergy and postoperative surgery) and Acular-PF (for pain and photophobia following refractive surgery). The nonclinical pharmacology, toxicology and PK studies have been previously reviewed in NDA 19-700 (Acular), NDA 20-811 (Acular PF), NDA 19-645 (oral formulation) and NDA 19-698 (injection formulation). Ketorolac tromethamathine ophthalmic solution 0.4% is a reformulation of Acular. The changes in the new formulation were limited to reductions in concentrations of ketorolac (0.4% vs. 0.5%), benzalkonium chloride (0.006% vs. 0.010%), EDTA (0.015% vs. 0.10%) and octoxynol-40 [redacted]) compared to Acular. It was agreed during the May 20, 2002 pre-NDA meeting that no new nonclinical pharmacology, PK and toxicology studies were necessary to support this NDA submission. Hence, in this NDA submission, the sponsor only submitted nonclinical study summaries and referred the studies to NDA 19-700 for Acular. For specific nonclinical studies, please refer to NDA 19-700 (ocular formulation), NDA 20-811 (ocular formulation), NDA 19-645 (oral formulation) and NDA 19-698 (injectable formulation).

I. PHARMACOLOGY:

Pharmacology summary and conclusions:

Systemic pharmacology studies have indicated that ketorolac is a potent analgesic and anti-inflammatory compound in rodent models in which inhibition of prostaglandin biosynthesis is active. Ketorolac has shown exceptional potency as an inhibitor of the cyclooxygenase pathway of arachidonate metabolism.

Ketorolac demonstrated potent anti-inflammatory activity when applied topically in several models of ocular inflammation. Ophthalmic ketorolac significantly inhibited the neovascularization response to silver nitrate-induced burns of the corneas of rat eyes at concentrations of 0.25% and 0.5%. Topical ketorolac solutions of 0.01%-0.5% blocked vascular permeability changes induced in the eye of rabbits by intravenous endotoxin (endotoxin-induced uveitis). Topical ketorolac (0.1%-0.5%) also blocked endotoxin-induced elevation of aqueous humor PGE_2. Ketorolac solutions (0.00001 - 0.1%) inhibited arachidonic acid-induced leakage of protein into the aqueous humor of rabbits with an IC50 of 0.00004%. Ketorolac 0.5% solution inhibited arachidonic acid-induced leakage of protein into the aqueous humor of rabbits and suppressed polymorphonuclear leukocyte migration into the cornea following the induction of keratitis. Ophthalmic formulations containing 0.5% ketorolac or 0.5% of the (-)-S-enantiomer of ketorolac inhibited lid closure and chemosis following application of a solution of sodium arachidonate to rabbit eyes. Ketorolac also prevented the development of increased intraocular pressure (IOP) induced in rabbits with topically applied arachidonic acid, while not affecting the IOP of normal eyes. An *in vivo* rabbit study demonstrated that topical 0.5% ketorolac did not appear to have a local anesthetic effect when applied to the eye.

Pharmacology conclusions:

When given systemically using rodent models, ketorolac demonstrated potent analgesic and anti-inflammatory activity, which was mediated primarily via inhibition of arachidonic acid

cyclooxygenase. When given topically, ketorolac demonstrated potent anti-inflammatory activity in several models of ocular inflammation in rats and rabbits.

II. SAFETY PHARMACOLOGY:

Please refer to Pharmacology/Toxicology reviews for NDAs 19-700, 20-811, 19-645, and 19-698.

III. PHARMACOKINETICS/TOXICOKINETICS:

PK/TK summary:

Relative bioavailability between two different radiolabeled formulations, one with BAK (benzalkonium chloride) and the other with thimerosal as preservatives, was measured in the anesthetized rabbit. The results showed that there were no significant differences between the formulations in C_{max}, AUC, and half-life of ketorolac. The half-life of ketorolac in ocular tissues was 4 – 6 hr. The absolute ocular bioavailability averaged 4% in both formulations. In an ocular distribution study in rabbits, higher concentrations of ketorolac were observed in the sclera and cornea than in the aqueous humor, vitreous humor, retina-choroid, iris-ciliary body, and lens. Systemic absorption of ketorolac after ocular administration in rabbits was rapid (Tmax = 15 min) with a half-life of 6.6-6.9 hr in the plasma, which was longer than intravenous administration (1.1 hr). In the monkey, the half-life in the plasma after ocular and intravenous administrations were similar, 1.8 and 1.6 hr respectively. No accumulation of drug was detected in aqueous humor and blood following 6 months of multiple ocular dosing in monkeys.

The majority of the ophthalmic dose was excreted in urine (rabbit: 66%; monkey: 75%) and a small amount in feces (rabbit: 11%; monkey: 2%). After ocular administration of radiolabeled drug to rabbits, 72%, 17% and 6% of the total radioactivity detected in the urine was characterized as parent drug, p-hydroxy ketorolac and other polar metabolites, respectively. After intravenous administration, 6%, 68% and 22% of the total radioactivity in the urine was characterized as parent drug, p-hydroxy ketorolac and other polar metabolites, respectively. In monkeys, after intravenous administration of radiolabeled drug, 32% and 65% of the total radioactivity in the urine was characterized as parent drug and a polar metabolite. After ocular administration, the urine comprised 50% and 49% of parent drug and the polar metabolite, respectively.

Relative bioavailability studies of 0.5% solution were performed between preserved and unpreserved formulations both *in vivo* and *in vitro*. In the *in vitro* studies, both intact corneas and de-epithelialized corneas were used. Ocular bioavailability increased significantly in the de-epithelialized corneas with the preserved formulation compared to unpreserved. There was no significant difference in ocular bioavailability between the preserved and non-preserved formulations when intact corneas were used. The apparent half-life in intact corneas was longer than that in the de-epithelialized corneas. In the aqueous humor, the AUC in the de-epithelialized cornea was higher with both formulations compared to that in intact corneas. The *in vivo* studies showed no significant difference in bioavailability between these two formulations.

The sponsor indicated that based on the similar composition of the formulation with reduced concentrations, the new formulation should be pharmacokinetically and pharmacodynamically similar to the original formulation. The reviewer agrees.

PK/TK conclusions:

Following ocular topical administration to rabbits and monkeys, ketorolac was rapidly absorbed in the ocular tissues and plasma. Higher drug concentrations were noted in cornea and sclera in rabbits. The half-life in the rabbit ocular tissues was 4-6 hr. The plasma half-lives of the drug were 6.6-6.9 hr and 1.8 hr in rabbits and monkeys, respectively. The majority of the ophthalmic dose was excreted in urine (rabbit: 66%; monkey: 75%) as parent drug, p-OH-ketorolac and other polar metabolites.

IV. GENERAL TOXICOLOGY:

Please refer to Pharmacology/Toxicology reviews for NDAs 19-700, 20-811, 19-645, and 19-698.

V. GENETIC TOXICOLOGY:

Please refer to Pharmacology/Toxicology reviews for NDAs 19-700, 20-811, 19-645, and 19-698.

VI. CARCINOGENICITY:

Please refer to Pharmacology/Toxicology reviews for NDAs 19-700, 20-811, 19-645, and 19-698.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Please refer to Pharmacology/Toxicology reviews for NDAs 19-700, 20-811, 19-645, and 19-698.

VIII. SPECIAL TOXICOLOGY STUDIES:

Summary:

Ketorolac ophthalmic solution was evaluated in rabbits (pigmented and nonpigmented) and monkeys with study duration up to 6 weeks and 12 months, respectively. No drug-related ocular toxicity was noted in these studies. Reversible, mild corneal effects (positive corneal fluorescein staining, thinning of the corneal epithelium, and corneal opacities) were noted among placebo and drug-treated pigmented rabbits using formulations containing BAK; however, these effects were attributable to the presence of BAK. These effects were not noted in similar studies with a thimerosal preservative in pigmented or albino rabbits, or in cynomolgus monkeys. The new 0.4% ketorolac tromethamine formulation contains reduced concentrations of BAK compared to the marketed Acular formulation, reducing the potential for the adverse effects. The safety of ketorolac ophthalmic solution was also evaluated in a rabbit model of photorefractive

keratectomy (PRK) followed by concurrent treatment with ketorolac ophthalmic solution (preserved or nonpreserved formulations) and placement of hydrophilic contact lenses for 7 days. There was no evidence of drug-related toxicity, adverse interaction with contact lenses, or impairment of corneal healing times observed.

Conclusions:

Ketorolac ophthalmic solution with the concentrations up to 4.0% induced no drug-related ocular and systemic toxicity in ocular toxicity studies performed in rats and monkeys with duration up to 6 weeks and 6 months, respectively. The study performed in a rabbit PRK model revealed no drug-related toxicity.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: Ketorolac tromethamine is an NSAID. The oral and injection formulations of the drug have been marketed for many years as an analgesic. Currently marketed topical ophthalmic ketorolac drug products include Acular (for allergy and postoperative surgery) and Acular-PF (for pain and photophobia following refractive surgery). Ketorolac tromethamine ophthalmic solution 0.4% is a reformulation of Acular. The changes in the new formulation (see table below) were limited to reductions in concentrations of ketorolac, benzalkonium chloride, EDTA, and octoxynol-40 compared to Acular.

Comparation of clinical formulations of ketorolac tromethamine ophthalmic solution 0.4% and Acular

Ingredient	ketorolac tromethamine ophthalmic solution 0.4%	Acular
Ketorolac tromethamine	0 4	0 5
Benzalkonium chloride, NF	0 006	0 01
Edetate disodium, USP	0 015	0 1
Octoxynol-40	[redacted]	
Sodium chloride, USP		[redacted]
NaOH, NF	pH 7 3-7 5	pH 7 3-7 5
HCl, NF	pH 7.3-7.5	pH 7.3-7 5
Purified water, USP	qs	qs

Acular (ketorolac tromethamine ophthalmic solution 0.5%) has been approved in the United States as a nonsteroidal analgesic anti-inflammatory ophthalmic agent since 1992 for the indication of temporary relief of ocular itching due to seasonal allergic conjunctivitis, and for the treatment of postoperative inflammation in patients who have undergone cataract extraction. The safety and efficacy of Acular have already been established. Ketorolac tromethamine ophthalmic solution 0.4% is indicated for the reduction of ocular pain and ocular symptoms of foreign body sensation, burning/stinging, tearing, and photophobia following refractive surgery. Phase 3 clinical studies showed that the drug was safe and effective. The proposed dosage for ketorolac tromethamine 0.4% is the same as Acular (1 drop, qid). The new formulation, contains reduced concentrations of the active ingredient, ketorolac tromethamine (from 0.5% to 0.4%), as well as the preservative and other excipients, should be safe for its intended use and might have less adverse effects.

General Toxicology Issues: No new nonclinical toxicology studies are necessary. No toxicological issues are indicated.

Recommendations:

Number of Pages Redacted 2

Draft Labeling
(not releasable)

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/s/

Zhou Chen
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PHARMACOLOGIST

Josie Yang
10/15/02 09:07:24 AM
PHARMACOLOGIST

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