

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-132

SUMMARY REVIEW

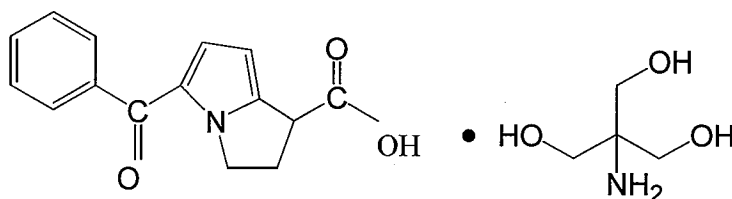
Division Director Memorandum for NDA 22-427

Date	July 20, 2009
From	Wiley A. Chambers, M.D.
NDA #	22-427
Applicant	Allergan, Inc.
Date of Submission	September 29, 2008
PDUFA Goal Date	July 31, 2009
Type of Application	505(b)(1)
Name	Acuvail (ketorolac tromethamine ophthalmic solution) 0.45%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Indicated for the treatment of pain and inflammation following cataract surgery
Action:	Approval

1. Introduction

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) which has demonstrated analgesic, anti-inflammatory, and antipyretic activity when administered systemically. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis. It has shown similar analgesic and anti-inflammatory effects in the eye.

Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% 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 its molecular weight is 376.41. Its molecular formula is $C_{19}H_{24}N_2O_6$. Its chemical structure is:



2. Background

Ketorolac been marketed as Acular (ketorolac tromethamine ophthalmic solution) 0.5%, Acular PF (ketorolac tromethamine ophthalmic solution) 0.5% [preservative free], and Acular LS (ketorolac tromethamine ophthalmic solution) 0.4%.

Acular is indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis and for the treatment of postoperative inflammation following cataract extraction. Acular has been marketed in the United States since 1992 for the treatment of inflammation and pain following cataract surgery. Acular PF is indicated for the reduction of ocular pain and photophobia following incisional

refractive surgery. Acular LS is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery but is not approved for postoperative inflammation following cataract extraction. The recommended dosage regimen for these other Acular products is 4 times daily.

Clinical studies 191578-005 and 191578-006 were conducted under IND 21,132. The efficacy endpoints chosen for the phase 3 studies have been widely used in clinical studies of ophthalmic solutions and are recognized as relevant for evaluation of the efficacy and safety of investigational products. The primary efficacy analysis was the comparison of the proportion of patients with clearing of anterior chamber inflammation between ketorolac 0.45% and vehicle after cataract surgery. Secondary efficacy variables included the proportion of patients with no postoperative ocular pain (i.e., grade of pain = 0) at both the morning and evening evaluation on day 1, and inhibition of surgically induced miosis as measured by the pupil area after irrigation and aspiration of the lens.

3. CMC

The drug substance ketorolac tromethamine is a white to off-white crystalline powder with a pKa of 3.49. It is a tromethamine $[\text{HOCH}_2\text{CNH}_2(\text{CH}_2\text{OH})_2]$ salt of ketorolac in a 1 to 1 molar ratio. The drug substance is freely soluble in water (>100 mg/mL) at room temperature and pH 6.8. Ketorolac tromethamine is manufactured at (b) (4) and is utilized for the current marketed product ACULAR, NDA 21-528.

The proposed drug product, ketorolac tromethamine ophthalmic solution 0.45%, is a sterile, non-preserved, clear, and colorless to pale yellow isotonic ophthalmic solution. This formulation contains 0.45% (w/v) ketorolac tromethamine. The inactive ingredients include carboxymethylcellulose (b) (4), (b) (4) sodium chloride (b) (4), and sodium citrate (b) (4). (b) (4) The pH of the bulk solution is adjusted using either 1N sodium hydroxide or 1N hydrochloric acid to a target pH of 6.8 for the final product. The drug product is packaged in clear, LDPE, unit dose vials in a 0.4 mL nominal fill volume/0.9 mL fill capacity. The drug product will be manufactured at Allergan America, Waco, Tx.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Ingredient	Concentration (% w/v)
Ketorolac Tromethamine	0.45
Carboxymethylcellulose (b) (4) (b) (4)	(b) (4)
Carboxymethylcellulose (b) (4) (b) (4)	(b) (4)
Sodium Chloride	(b) (4)
Sodium Citrate Dihydrate	(b) (4)
Sodium Hydroxide	Adjust to pH 6.8
Hydrochloric Acid	Adjust to pH 6.8
Purified Water	(b) (4)

PROPOSED REGULATORY SPECIFICATIONS:

Drug Product Specifications for Ketorolac Tromethamine Ophthalmic Solution 0.45%

Test	Release	Shelf	Method
Physical Appearance	Clear, colorless to pale yellow solution	Clear, colorless to pale yellow solution	AP-MS010
pH		(b) (4)	USP <791>
Ketorolac Tromethamine HPLC Assay			AP-L236
ID Test			
Ketorolac Tromethamine (HPLC)			AP-L236
Ketorolac Tromethamine (UV)			ASET-DP-ID074
Osmolality			USP <785>
Ketorolac Tromethamine Impurities (%w/w): Specified and Identified		(b) (4)	AP-L236
Particulate Matter (Count)	(b) (4) (b) (4) (b) (4)	(b) (4)	AP-Z003 USP <789>
Leachables: Specified and Identified	(b) (4)		Volatile and Semi-Volatile Organic Leachable Compounds from (b) (4)
Microbiology: Sterility	Meets compendial acceptance criteria	Meets compendial acceptance criteria	USP <71>
Viscosity	(b) (4)	(b) (4)	AP-V008
Bacterial Endotoxin	(b) (4)	(b) (4)	Section 3.2.P.5.2 Analytical Procedure Endotoxin (b) (4)

FACILITIES INSPECTIONS:

The overall recommendation from the Office of Compliance is "Acceptable" in EES.

4. Nonclinical Pharmacology/Toxicology

Nonclinical Pharmacology and Toxicology information was referenced from prior submissions from the applicant. The data has been incorporated into the labeling as listed below. Ketorolac tromethamine was not carcinogenic in either rats given up to 5 mg/kg/day orally for 24 months or in mice given 2 mg/kg/day orally for 18 months. These doses are approximately 900 times and 300 times higher respectively than the typical human topical ophthalmic daily dose given as BID to an affected eye on a mg/kg basis.

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 9 mg/kg/day and 16 mg/kg/day, respectively. These doses are respectively 1500 and 2700 times higher than the typical human topical ophthalmic daily dose.

5. Clinical Pharmacology/Biopharmaceutics

Differences in the product's formulation versus the approved Acular products include a lower pH, removal of benzalkonium chloride (BAK), edetate disodium, and octoxynol-40, and the addition of carboxymethylcellulose (CMC). No clinical pharmacology studies were submitted in this application. A waiver of the requirement for submission of evidence of *in vivo* bioavailability is granted since the systemic exposure of ketorolac following ophthalmic administration of Acuvail is not expected to exceed that of Acular and is expected to be low in comparison to exposures observed following systemically administered ketorolac tromethamine, as evidenced by pharmacokinetic information available for currently marketed ketorolac-containing ophthalmic products.

Per 21 CFR 320.22 (e), a waiver of the requirement for submission of evidence of *in vivo* bioavailability is granted for the proposed drug product Acuvail (ketorolac tromethamine ophthalmic solution) 0.45%. Information on previously approved and marketed ketorolac formulations supports this recommendation.

6. Sterility Assurance

There are no microbiology deficiencies identified. A kinetic turbidimetric LAL test will be used to test the drug product for endotoxin. The endotoxin limit is NMT (b) (4). The kinetic turbidimetric test method was validated by performing inhibition/enhancement testing with the drug product. A (b) (4) dilution allowed an endotoxin recovery that met the (b) (4) acceptance criteria. The (b) (4) dilution will be used for testing the drug product.

A membrane filtration method is used for sterility testing of the finished drug product. The method is based on USP <71>. The method was validated for use with the drug product by performing bacteriostasis/fungistasis testing.

7. Clinical/Statistical - Efficacy

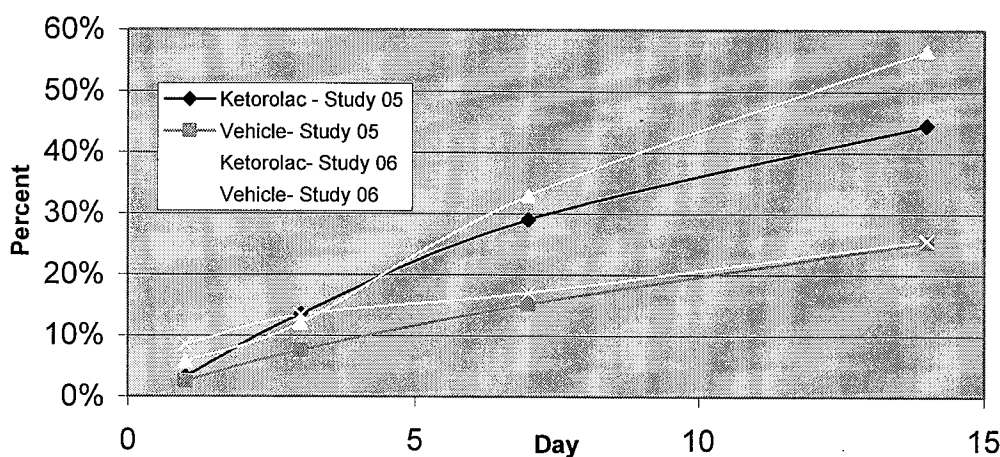
Efficacy was demonstrated in two adequate and well controlled studies which demonstrated that more patients treated with Acuvail (than vehicle) had no observed inflammation 14 days after cataract surgery.

Anterior Chamber Cells		Anterior Chamber Flare	
Grade Score	Cell Count	Grade Score	Flare
0	0 cells	0	None: No flare seen
+0.5	1-5 cells (trace)	+1	Faint: Faint flare seen
+1	6-15 cells	+2	Moderate: Iris and lens details clear
+2	16-25 cells	+3	Marked: Iris and lens details hazy
+3	26-50 cells	+4	Intense: Fibrin or plastic aqueous
+4	> 50 cells		

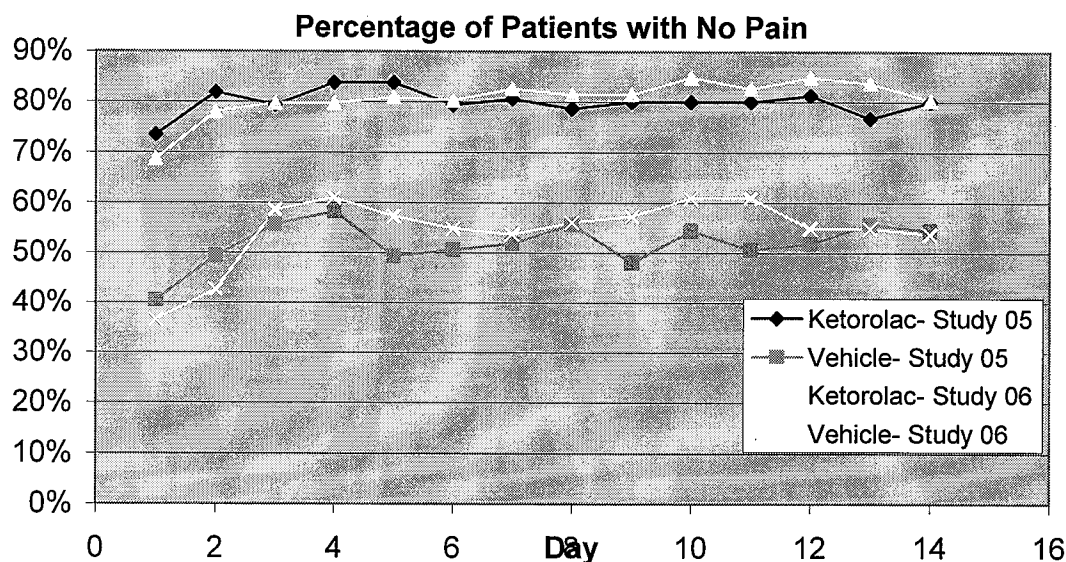
The following secondary efficacy measures were evaluated:

- Ocular pain as measured by a twice daily self-assessment by the patient within approximately 1 hr after dosing using a 5-point grade scale (0 = none, +1 = mild, +2 = moderate, +3 = severe, +4 = intolerable) was assessed. The percentage of patients with no pain (grade = 0) on day 1 was evaluated as a secondary efficacy analysis.
- Horizontal and vertical pupil diameters were measured immediately pre-incision, post-I&A of the lens, and after IOL placement. The mean pupil area post-I&A of the lens was evaluated as a secondary efficacy analysis.

Percentage of Patients with Inflammation Cleared (ITT)



The results of each study were statistically significant at day 14 ($p=0.002$).



Inhibition of Surgically Induced Miosis

Study 05- The mean pupil area measured post-I&A was not statistically significantly different between the two treatment groups ($p = 0.706$). Mean pupil area post-I&A was 41.8 mm² in the ketorolac 0.45% group and 41.1 mm² in the vehicle group.

Study 06- The mean pupil area measured post-I&A was not statistically significantly different between the two treatment groups ($p = 0.413$). Mean pupil area post-I&A was 37.9 mm² in the ketorolac 0.45% group and 36.5 mm² in the vehicle group.

Efficacy Summary

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that patients receiving Acuvail had a significantly higher incidence of clearing of anterior chamber inflammation versus patients receiving vehicle at day 14. Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% was also significantly superior to vehicle in resolving ocular pain on Day 1 post cataract surgery. There is not substantial evidence that Acuvail is effective in the inhibition of surgically induced miosis following cataract extraction with posterior chamber intraocular lens implantation.

8. Safety

The patient exposure and safety assessments were adequate. No patient or subject deaths occurred during the conduct of the two Phase 3 clinical studies and the additional safety study that form the basis of this application.

Serious Adverse Events by Treatment (Pooled)

Study-Subject	Age/Sex Race	Eye	Abbrev. SOC	Preferred Term\ Investigator Term	Onset/Max Severity\ Related to Study Drug/ Led to Discontinua- tion	Onset Day\ Duration	Seriousness Criteria
Treatment: Ketorolac 0.45%							
191578006-10002-1163	62/Male	Non-ocular	Inj&P	Post procedural haemorrhage	Severe/Severe	7	Hospitalization
	Caucasian			Post Colonoscopy intestinal bleeding	No/No	3	
191578003-10006-1270	69/Male Caucasian	Non-ocular	Card	Angina unstable unstable angina	Severe/Severe No/Yes	18 -----	Hospitalization
191578003-10015-1182	72/Male Caucasian	Non-ocular	Card	Cardiac arrest asystole	Severe/Severe No/Yes	12 1	Life-Threatening, Hospitalization
		Non-ocular	Card	Coronary artery occlusion coronary artery blockage	Severe/Severe No/Yes	13 1	Hospitalization
Treatment: Vehicle							
191578003-10011-1048	55/Male	Non-ocular	Card	Coronary artery disease	Severe/Severe	4	Life-Threatening, Hospitalization
	Caucasian			Coronary Artery Disease	No/Yes	6	

Source: ISS Table 2.7.4.7-13.2; Listing 14.3.2 (Reports 191578-005 and -006); Listing 16.2.7-1 (Reports 191578-005 and -006)

SOC = abbreviated System Organ Class of MedDRA; Card = Cardiac disorders; Inj&P = Injury, poisoning and procedural complications

Four patients in the pooled phase 3 studies and none in the phase 1 study experienced serious adverse events. All of the serious adverse events were non-ocular in nature.

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Adverse Events by Decreasing Incidence: Phase 3 Clinical Studies, Pooled (Safety Population)

Adverse Event (Preferred Term) ^a n (%)	SOC Abbrev.	Ketorolac 0.45% (N=330)	Vehicle (N=163)
Overall		116 (35.2)	79 (48.5)
Intraocular pressure increased	Inv	19 (5.8)	3 (1.8)
Anterior chamber cell	Eye	17 (5.2)	10 (6.1)
Conjunctival hyperaemia	Eye	15 (4.5)	23 (14.1)
Eye pain	Eye	14 (4.2)	25 (15.3)
Iritis	Eye	14 (4.2)	12 (7.4)
Anterior chamber flare	Eye	12 (3.6)	8 (4.9)
Corneal oedema	Eye	11 (3.3)	10 (6.1)
Foreign body sensation in eyes	Eye	11 (3.3)	9 (5.5)
Headache	Nerv	10 (3.0)	6 (3.7)
Lacrimation increased	Eye	4 (1.2)	4 (2.5)
Conjunctival haemorrhage	Eye	4 (1.2)	1 (0.6)
Vision blurred	Eye	4 (1.2)	1 (0.6)
Photophobia	Eye	3 (0.9)	16 (9.8)
Conjunctival oedema	Eye	3 (0.9)	4 (2.5)
Eye irritation	Eye	3 (0.9)	4 (2.5)
Eye pruritus	Eye	3 (0.9)	3 (1.8)
Corneal abrasion	Inj&P	3 (0.9)	1 (0.6)
Vitreous detachment	Eye	3 (0.9)	1 (0.6)
Posterior capsule rupture	Eye	3 (0.9)	0 (0.0)
Vitreous floaters	Eye	3 (0.9)	0 (0.0)
Anterior chamber fibrin	Eye	2 (0.6)	2 (1.2)
Cataract operation complication	Inj&P	2 (0.6)	1 (0.6)
Macular oedema	Eye	2 (0.6)	1 (0.6)
Nausea	Gastr	2 (0.6)	1 (0.6)
Punctate keratitis	Eye	2 (0.6)	1 (0.6)
Anterior chamber inflammation	Eye	1 (0.3)	6 (3.7)
Iris haemorrhage	Eye	1 (0.3)	2 (1.2)
Eyelid oedema	Eye	0 (0.0)	3 (1.8)
Facial pain	Genrl	0 (0.0)	3 (1.8)
Uveitis	Eye	0 (0.0)	3 (1.8)

Source: ISS Table 2.7.4.7-9.2

SOC = abbreviated System Organ Class of MedDRA; Eye = eye disorders; Inv = investigations; Nerv = nervous system disorders; Inj&P = injury, poisoning and procedural complications; Gastr = gastrointestinal disorders; Genrl = general disorders and administration site conditions

a Adverse events occurring in 3 or more patients

The most common adverse events were reported in 1-6% of patients and included increased intraocular pressure, conjunctival hyperemia and/or hemorrhage, corneal edema, ocular pain, headache, tearing and vision blurred. Some of these events may be the consequence of the cataract surgical procedure.

Safety Summary

There is substantial evidence of safety consisting of adequate and well controlled studies which demonstrate that Acuvail, dosed twice a day, is safe for the treatment of pain and inflammation following cataract surgery.

The most common adverse events were reported in 1-6% of patients and included increased intraocular pressure, conjunctival hyperemia and/or hemorrhage, corneal edema, ocular pain, headache, tearing and vision blurred. Some of these events may be the consequence of the cataract surgical procedure.

9. Advisory Committee Meeting

No Advisory Committee was necessary or convened for this drug product.

10. Pediatrics

Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients. In accordance with CFR 314.55(c)(2)(i), Allergan, Inc. requested a waiver for Pediatric Studies in all patients (neonates, infants, children, and adolescents) from birth to 16 years of age.

In patients less than 6 months of age, the cataract is most often removed under anesthesia. The preferred procedure is lensectomy with vitrectomy, with or without IOL placement. Postoperative inflammation in the absence of IOL implantation is generally includes topical mydriatic, anti-infective, and steroid medications.

Allergan previously submitted a Pediatric Study Report to the Agency on 18 June 2001 for NDA 19-700 and NDA 20-811 which was done with the same active ingredient, ketorolac tromethamine, formulated at 0.5% in pediatric patients between 3 and 12 years of age. This pediatric study was subsequently accepted by the Agency on 8 February 2002 and pediatric exclusivity was granted to the abovementioned NDAs. The current application for ketorolac tromethamine ophthalmic solution 0.45% uses the same active ingredient, at a lower concentration and lower dosing frequency (BID compared to QID) as that of the 0.5% formulation for which a pediatric clinical trial has been completed.

11. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested. The sites requested for inspection were the centers with the largest number of enrolled patients in the pivotal studies that had no prior inspection history. Three clinical investigator inspections have been completed for this NDA. Based on the results of these inspections, the study appears to have been conducted adequately and the data in support of the NDA appear reliable (with the exception of data from two subjects at Dr. Gurevich's site). No regulatory violations were noted for Dr. Reiser or Dr. Alpern. A Form FDA 483 was issued to Dr. Gurevich. However, based on DSI's discussion of the issues with the review division it appears that the nature of the violations makes it unlikely that they significantly affect overall reliability of safety and efficacy data from this site, with the exception of data from two subjects (#1174 and #1183). These subjects received prohibited concomitant medications when they had cataract surgery on the other eye within 7 days of study eye surgery.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA

In an email dated June 25, 2009, the Division of Medication Error Prevention and Analysis (DMEPA) noted it had completed evaluation of the proposed proprietary name Acuvail (Ketorolac tromethamine Ophthalmic Solution). They were concerned that Acuvail may be confused with a product in the pipeline that may render the name unacceptable. Acuvail is vulnerable to name confusion that could lead to medication errors with the name (b) (4), which is a pending application within the Agency. DMEPA provided recommendations on the packaging configuration and the package insert labeling. These are incorporated into the Medical Officer's labeling where appropriate.

DDMAC

In a review finalized 7/9/09, DDMAC has reviewed the proposed product labeling, including the package insert (PI), draft carton label, draft container vial, and the draft container pouch for Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% submitted by the applicant on September 29, 2008; they also took into consideration the labeling for Acular LS (ketorolac tromethamine ophthalmic solution), Xibrom (bromfenac sodium ophthalmic solution), and Nevanac (nepafenac ophthalmic suspension). Where appropriate, these recommendations have been incorporated into the final labeling for the product.

BIOSTATISTICS

The Statistical Review concurred with the finding listed in the Clinical Efficacy above.

12. Labeling

NDA 22-427, Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% as amended has been recommended for approval for the treatment of pain and inflammation following cataract surgery labeling found in the Appendix at the end of this CDTL review.

13. Regulatory Action

NDA 22-427, Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% can be approved for the treatment of pain and inflammation following cataract surgery.

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that patients receiving Acuvail had a significantly higher incidence of clearing of anterior chamber inflammation versus patients receiving vehicle at day 14. Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% was also significantly superior to vehicle in resolving ocular pain on Day 1 post cataract surgery.

The most common adverse events were reported in 1-6% of patients and included increased intraocular pressure, conjunctival hyperemia and/or hemorrhage, corneal edema, ocular pain, headache, tearing and vision blurred. Some of these events may be the consequence of the cataract surgical procedure.

Pharmacology/Toxicology, CMC, Biostatistics, Clinical, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application.

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products

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/s/

Wiley Chambers
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