CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-528

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 21-528
Original

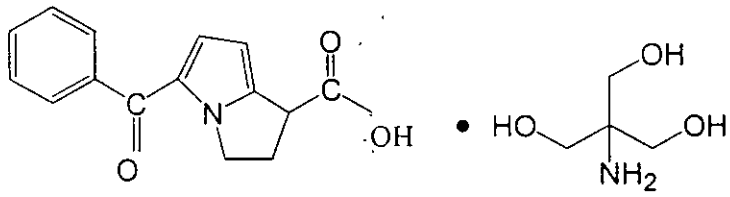
NDA 21-528
Medical Officer's Review

Submission Date: August 6, 2002
Review Completed: January 15, 2003

Proposed Trademark: To be determined

Generic Name: Ketorolac tromethamine ophthalmic solution 0.4%

Chemical Name:



Mol Wt 376.41
ketorolac tromethamine $C_{19}H_{24}N_2O_6$

(±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

Sponsor:

Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534
(714) 246-4391
Contact: Elizabeth Bancroft

Pharmacologic Category: Nonsteroidal anti-inflammatory

Related IND:

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Executive Summary

1 Recommendations

1.1 Recommendation on Approvability

NDA 21-528 is recommended for approval for the reduction of post-operative pain and burning/stinging following photorefractive keratecotomy (PRK) surgery.

1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

No additional Phase 4 studies and/or risk management steps are recommended.

2 Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug. Ketorolac tromethamine ophthalmic solution (Acular) 0.5% is approved for the temporary relief of ocular itching due to seasonal allergic conjunctivitis and the treatment of postoperative inflammation in patients who have undergone cataract extraction. Ketorolac tromethamine ophthalmic solution (Acular PF) 0.5% Presevative-Free is approved the reduction of ocular pain and photophobia following incisional refractive surgery. Ketorolac tromethamine ophthalmic solution 0.4% is a reformulation of Acular which contains 0 5% of ketorolac tromethamine.

In this submission, NDA 21-528, the Applicant has submitted two clinical studies (191578-002 and 191578-003) in support of the proposed indication: the reduction of ocular pain [redacted] burning/stinging, [redacted] following refractive surgery.

2.2 Efficacy

The submitted studies in NDA 21-528 are sufficient to establish efficacy for the use of ketorolac 0.4% in the reduction of post-operative pain and burning/stinging following PRK surgery.

2.3 Safety

The safety data contained in this submission is comparable to that reported for previously approved ketorolac tromethamine ophthalmic solutions, NDA 19-700 (Acular 0.5%) and NDA 20-811 (Acular PF 0.5%).

2.4 Dosing

The dosing regimen proposed in this submission is one drop four times a day in the operated eye as needed for up to 4 days following PRK surgery.

2.5 Special Populations

No additional data on special populations are needed.

Clinical Review

1 Introduction and Background

1.1 Proposed Trademark: To be determined.

Generic Name: Ketorolac tromethamine ophthalmic solution 0.4%

NDA Drug Classification: 3S

Proposed Indication: Reduction of ocular pain and [redacted], burning/stinging. [redacted] following refractive surgery

Dosage Form and Route of Administration: Ophthalmic solution for topical ocular Administration

Age Groups: Adults 18 years of age or older

1.2 Ketorolac tromethamine is a nonsteroidal anti-inflammatory agent. Acular PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free is approved for the reduction of ocular pain and photophobia following incisional refractive surgery. Voltaren ophthalmic (diclofenac sodium ophthalmic solution) 0.1% is another topical nonsteroidal anti-inflammatory agent that is approved for temporary relief of pain and photophobia in patients undergoing refractive surgery.

1.3 The agency requested the applicant to perform safety and efficacy analyses with and without data from study site #3753 (Investigator Frank Bishop) because Investigator Bishop was deemed not qualified to served as a principle investigator in clinical protocol 191578-002.

The applicant agreed to perform a sensitivity analysis analyzing pain intensity for the intent-to-treat population with and without data from study site #3508 for clinical protocol 191578-003, to demonstrate that the protocol deviations associated with this study site did not adversely impact the data.

1.4 Acular (ketorolac tromethamine ophthalmic solution) 0.5% and Acular PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free are approved products and currently marketed in the United States. Ketorolac tromethamine ophthalmic solution (ketorolac) 0.5% has been reformulated with a lower concentration (0.4%) of the active ingredient, ketorolac tromethamine.

1.5 There are no safety and effectiveness concerns associated with agents in this pharmacologic class.

2 Significant Findings from Chemistry, Animal Pharmacology and Toxicology, and/or Microbiology

Agree with Chemistry's and Animal Pharmacology and Toxicology's recommendations. See Chemistry and Animal Pharmacology and Toxicology Reviews for detailed results.

3 Human Pharmacokinetics and Pharmacodynamics

3.1 See Clinical Pharmacology and Biopharmaceutics Review. No new issues.

3.2 See Clinical Pharmacology and Biopharmaceutics Review. No new issues.

4 Description of Clinical Data and Sources

4.1 Included in this medical officer's review are evaluations of two clinical trials conducted in the United States under [redacted]

4.2 See Table 1 for a descriptive summary of the clinical trials.

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Table 1 – Description of Data Sources

Protocol Number	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	No. Sites	No. Subjects Randomized	Status
Phase 3 Studies								
Safety/Efficacy 191578-002 U.S.	Randomized, double-masked, vehicle-controlled	Up to 4 days	Post-[a]PRK patients	[b]Ketorolac [c]Vehicle	1 drop QID in study eye	8	156 (1:1)	Completed
Safety/Efficacy 191578-003 U.S.	Randomized, double-masked, vehicle-controlled	Up to 4 days	Post-[a]PRK patients	[b]Ketorolac [c]Vehicle	1 drop QID in study eye	7	157 (1:1)	Completed

[a]Photorefractive keratectomy
[b]Ketorolac tromethamine ophthalmic solution 0.4%
[c]Vehicle of ketorolac tromethamine ophthalmic solution 0.4%

4.3 No new safety information from post-marketing experience are available.

4.4 There are not any data in the published literatures that are pertinent to the review of this submission.

5 Clinical Review Methods

5.1 This medical officer's review evaluated each of the two clinical trials separately.

5.2 The submission is provided in paper and electronic formats. The review relied on the paper and electronic copies.

5.3 The Division of Scientific Investigations plans to audit three sites (study site #3753 for protocol 191578-002 and study sites #3508 and #1345 for protocol 191578-003).

5.4 There is no evidence to indicate that the trials were not conducted in accordance with accepted ethical standards.

5.5 Financial disclosure statements are submitted. There is no evidence to indicate that participation of investigators who have financial arrangements with the applicant affected the integrity of the findings.

6 Integrated Review of Efficacy

6.1 The submitted studies in NDA 21-528 are sufficient to establish efficacy for the use of ketorolac 0.4% in the reduction of post-operative pain following PRK surgery.

The submitted studies in NDA 21-528 are sufficient to establish efficacy for the use of ketorolac 0.4% in the reduction of burning/stinging following PRK surgery.

The submitted studies in NDA 21-528 are not sufficient to establish efficacy for the use of ketorolac 0.4% in the reduction of foreign body sensation, photophobia, and tearing following PRK surgery.

6.2 The efficacy database consists of efficacy data from two clinical trials, Protocols 191578-002 and 192578-003.

6.3.1 **Proposed Indication #1:** The reduction of ocular pain following refractive surgery.

Study #1 Protocol No. 191578-002 Conducted 8/24/01 to 12/31/01

Title: A Multi-center, Randomized, Double-masked, Vehicle-controlled, Parallel-Group Study Evaluating the Safety and Analgesic Efficacy of Ketorolac Tromethamine 0.4% Ophthalmic Solution in Post-Photorefractive Keratectomy Patients

Study Design: A multi-center, randomized, double-masked, vehicle-controlled, parallel-group study.

Test Drug Schedule: Patients received one drop of masked study medication immediately post-operatively, 3 hours post-operatively, and than every 4 hours while patient was awake, not to exceed 4 doses. For the next three days, patient self-administered one drop of masked study medication 4 times daily.

Investigator Number	Investigator	Number Randomized
3753	**Frank M. Bishop, M.D.** San Diego, CA 92134 USA	37
1538	**Roy S. Chuck, M.D., Ph.D.** Irvine, CA 92697 USA	7
3751	**Eric D. Donnenfeld, M.D.** Rockville Centre, NY 11570 USA	31
3379	**Barry Katzman, M.D.** San Diego, CA 92115 USA	24
3834	**Sylvia W. Norton, M.D.** Syracuse, NY 13210 USA	18
2226	**Michael B. Raizman, M.D.** Boston, MA 02114 USA	13
2947	**Robert W. Snyder, M.D., Ph.D.** Tucson, AZ 85711 USA	7
2298	**Richard W. Yee, M.D.** Houston, TX 77030 USA	19

Reviewer's Comments:

It is preferable to have at least 10 patients per arm per center.

I. Study Design

This was a multi-center, randomized, double-masked, vehicle-controlled, parallel group study designed to evaluate the safety and efficacy of ketorolac 0.4% as compared to vehicle of ketorolac 0.4% (vehicle) in the reduction of post-operative pain following unilateral PRK surgery.

Patients who, in the opinion of the investigator were candidates for unilateral PRK surgery within 7 days after visit 1 and met all inclusion/exclusion criteria were eligible to enter the study. Patients who enrolled were randomized to receive either masked ketorolac 0.4% or vehicle in a 1:1 allocation.

At visit 2, patients underwent PRK surgery, followed immediately by administration of 1 drop of masked study medication in the study eye. Patient was instructed to self-administer 1 drop of masked study medication approximately 3 hours post-operatively, and then every 4 hours while awake up to a total of 4 doses. On visits 3 through 5, patients self-administered masked study medication 4 times daily.

Patients were instructed to administer 1 drop of Ocuflox in the study eye approximately 5 minutes prior to each dose of study medication. Escape medication (——— ———) was to be administered as needed (one tablet up to every 4 hours) for intolerable pain during the treatment period.

During the treatment period, patients recorded, in electronic diaries, pain intensity immediately before each dose of Ocuflox and escape medication and pain relief approximately 2 hours after taking each dose of study medication.

Study Medications

- Ketorolac tromethamine ophthalmic solution 0.4% (Allergan formulation number 9437X; 10mL bottle with 5 mL fill volume). Contained 0.4% keterolac tromethamine (4 mg/mL), benzalkonium chloride 0.006%, edetate disodium 0.015%, octoxynol ——— , sodium chloride ——— , hydrochloric acid and/or sodium hydroxide to adjust the pH to 7.4, and purified water (manufactured by Allergan).
- Vehicle of ketorolac tromethamine ophthalmic solution 0.4% (Allergan formulation number 9439X; 10 mL bottle with 5 mL fill volume) contained benzalkonium chloride 0.006%, edetate dosodium 0.015%, octoxynol ——— , sodium chloride ——— , hydrochloric acid and/or sodium hydroxide to adjust the pH to 7.4 and purified water (manufactured by Allergan).

Inclusion Criteria

The following were requirements for entry into the study:

1. Male or female 18 years of age or older.

2. In the opinion of the investigator, a candidate for unilateral PRK surgery within the 7 days after visit 1 (day –7 to day –1).
3. Best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity equivalent to a Snellen score of 20/100 or better in each eye.
4. Agreement by women of child-bearing potential to use reliable method of birth control during study participation.
5. Documentation of informed consent.
6. Capable of wearing a soft bandage contact lens.

Visit 2 (day 0):

1. Willingness and demonstrated ability to use electronic diary.
2. Demonstrated ability to apply study treatment (masked medication and Ocuflox).

Exclusion Criteria

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

1. History of refractive ocular surgery in either eye.
2. Sensitivity or poor tolerance to any component of the masked study treatments, any NSAIDs, actaminophen, codeine, or any other component of [redacted] #3, and fluoroquinolones including Ocuflox.
3. Pregnancy, nursing, or attempting to become pregnant.
4. Uncontrolled systemic disease.
5. Anticipated use of alcohol or other central nervous system depressants during the study.
6. Patient had a condition or was in a situation which, in the investigator's opinion, may have put the patient at significant risk, may have confounded the study results, or may have interfered significantly with the patient's participation in the study.

Visit 2 (day 0):

1. Clinically significant operative complication from PRK surgery performed.
2. Use of the following medications within 7 days prior to visit 2 (day 0): analgesics (including acetaminophen or NSAIDs), corticosteroids, anti-coagulants, long-acting anticholinergics (e.g. atropine, scopolamine, homatropine), narcotic analgesics, antipsychotics, antianxiety agents, or other central nervous system depressants (including alcohol); short-acting mydriatics (e.g. [redacted] were permitted for dilated eye exam and refraction.
3. Use of an investigational product within the 30 days prior to visit 2 (day 0).

Efficacy Variables

The primary efficacy variable was maximum pain intensity score using a 5-point scale during the first 12-hour post PRK surgery. Pain intensity was recorded on electronic diaries immediately before each dose of Ocuflox and prior to use of escape medication.

The secondary efficacy variables were pain intensity rating during all other 12-hour periods post PRK surgery, pain relief following use of masked medication, escape medication usage, and ocular symptoms (foreign body sensation, photophobia, burning/stinging, tearing, and itching).

Safety Variables

The following safety variables were assessed:

1. Adverse events
2. Biomicroscopy
3. Visual acuity
4. Corneal re-epithelialization

Schedule of Visits and Procedures

Study Procedure	Visit 1	Visit 2 (PRK)	Visit 3	Visit 4	Visit 5[f]	Visit 6+[f]
	Treatment Period					Post-Treatment
	Day -7 to -1	Day 0	Day 1	Day 2	Day 3	Day 4-
Informed consent	X					
Medical & ophthalmic history	X					
Best-corrected visual acuity[a]	$X_{Both\ Eyes}$				$X_{Study\ Eye}$	X
Biomicroscopy[a]	$X_{Both\ Eyes}$		$X_{Study\ Eye}$	$X_{Study\ Eye}$	$X_{Study\ Eye}$	X
Ocular symptoms questionnaire	X		X	X	X	X
Escape medication[g]		Dispense	Review	Review	Review Collect	Review Collect
Pregnancy test		X				
Patient diary[b,h] Pain intensity Pain escape Escape medication	Dispense	Review	Review	Review	Review Collect	
Masked study[c,h] treatment		Dispense	Review	Review	Review Collect	
Ocuflox[c,g]		Dispense	Review	Review	Review Collect	Review Collect
Assess adverse events		X[d]	X	X	X	X
Assess concomitant medications		X	X	X	X	X

[a] Best-corrected visual acuity and biomicroscopy will be assessed o both eyes at visit 1 (Days -7 to -1), and on the study eye only at subsequent visits (as indicated above).

[b] Patients will electronically record pain intensity on the Patient Diary immediately prior to each instillation of Ocuflox Pain relief will be recorded by the patient approximately 2 hours after each instillation of masked study treatment. The time of diary entry for pain intensity and pain relief data will also be recorded. Time to escape medication use, along with pain intensity immediately prior to escape medication dosing, will also be recorded electronically on the Patient Diary The time of each masked study treatment dosing will be recorded as well. Entries into the electronic diary will be made through visit 5 (Day 3), at

which time the diaries will be collected. Pain will be collected on the Ocular Symptom Questionnaire during the post-treatment period.

[c] If complete re-epithelialization is not identified at visit 5 (Day 3), daily visits will continue until complete re-epithelialization is identified. These additional visits will comprise the post-treatment follow-up period.

[d] Assessment of Adverse Events will occur after instillation of study treatment at visit 2 (Day 0)

[e] Patient will stop taking study medication and Ocuflox prior to visit 5 (Day 3) if complete re-epithelialization is identified and a pain intensity rating equal to zero on the electronic diary is confirmed at a study visit. If re-epithelialization has not occurred by visit 5 (Day 3), Ocuflox may be administered without subsequent administration of masked study medication during the post-treatment period until re-epithelialization occurs, at which time the patient will exit the study.

[f] If re-epithelialization has occurred by visit 5 (Day 3), then the patient will exit the study. If pain persists after visit 5 (Day 3), and re-epithelialization has occurred, the patient will exit the study and will be treated at the discretion of the investigator.

[g] Ocuflox and escape medication will be collected at each patient's final visit.

[h] Electronic patient diaries and masked study treatment will be collected at visit 5 (Day 3), or earlier, if patient exits the study

Subject Disposition and Demographics

All 156 randomized subjects received treatment and 147 subjects completed the study.

Subject Disposition

	Number of Subjects		
	Ketorolac 0.4% N (%)	Vehicle N (%)	Total N (%)
Randomized	77	79	156
Discontinued prematurely	5 (6.5)	4 (5 1)	9 (5 8)
Included in safety evaluations	77 (100.0)	79 (100 0)	156 (100.0)
Included in intent-to-treat efficacy analysis	77 (100.0)	79 (100.0)	156 (100 0)
Included in per protocol efficacy analysis	65 (84.4)	60 (75.9)	125 (80 1)

Summary of Reasons for Premature Discontinuation from Study

	Number (%) of Subjects		
	Ketorolac 0.4% (N=77 N (%)	Vehicle (N=79) N (%)	Total (N=156) N (%)
Adverse events	5 (6.5)	2 (2 5)	7 (4 5)
Protocol violations		1 (1 3)	1 (0 6)
Administrative reasons		1(1.3)	1 (0 6)
Total	5 (6.5)	4 (5.1)	9 (5 8)

Discontinued Patients and Reasons

Investigator	Patient	Treatment	Reason
3751	1009	Ketorolac 0.4%	Adverse events – eye pain, excessive dosing with escape medication
	1014	Ketorolac 0.4%	Adverse events – corneal infiltrates
	1133	Ketorolac 0.4%	Adverse events – eye pain, excessive dosing with escape medication
	1134	Ketorolac 0.4%	Adverse events – eye pain, excessive dosing with escape medication
	1129	Vehicle	Adverse events – eye pain
3753	1087	Ketorolac 0.4%	Adverse events – eye pain, excessive dosing with escape medication
	1097	Vehicle	Administrative – inability to continue
	1101	Vehicle	Adverse events – ocular irritation
2298	1026	Vehicle	Protocol violation – non-compliance

Summary of Demographic Characteristics (Intent-to-Treat)

		Ketorolac) 0 4% (N=77)	Vehicle (N=79)	Total (N=156)	p-value [a]
Age (Years)	N	77	79	156	0 590
	Mean	40 4	39 4	39 9	
	SD	10.69	10.64	10.64	
	Median	38.0	38.0	38.0	
	Min	18	23	18	
	Max	66	64	66	
Sex	N	77	79	156	0.343
	Male	40 (51 9%)	47 (59.5%)	87 (55.8%)	
	Female	37 (48.1%)	32 (40.5%)	69 (44.2%)	
Race	N	77	79	156	0.189
	Caucasian	64 (83.15)	67 (84 8%)	131 (84 0%)	
	Black	3 (3.9%)	8 (10.1%)	11 (7.1%)	
	Asian	4 (5 2%)	2 (2.5%)	6 (3 8%)	
	Hispanic	6 (7 8%)	2 (2.5%)	8 (5 1%)	
Eye Color	N	77	79	156	0.420
	Blue	32 (41.6%)	23 (29.1%)	55 (35.3%)	
	Brown	29 (37.7%)	37 (46.8%)	66 (42.3%)	
	Green	5 (6.5%)	6 (7.6%)	11 (7.1%)	
	Hazel	10 (13.0%)	13 (16.5%)	23 (14.7%)	
	Other [b]	1 (1.3%)	0 (0.0%)	1 (0.6%)	

[a] p-value for age is from Wilcoxon rank sum test.
p-values for sex, race, and iris color are from Pearson's chi-square test (or Fisher's exact if >50% of cells have expected count <5).
[b] 'Other' iris color includes 'grey'

Efficacy **Intent-to-Treat Population**

Efficacy analyses with and without data from study site #3753 (Principal Investigator – Frank Bishop) were performed.

The following analyses include data from study site #3753:

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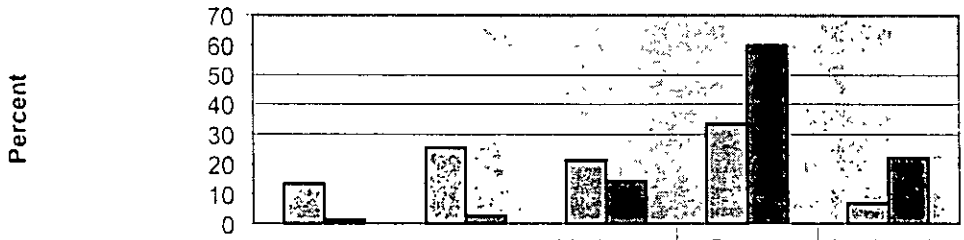
First 12-hour Post-PRK Period Pain Intensity Scores
(Primary Efficacy)

Percent of Subjects in Each Pain Severity Category



	No Pain	Mild Pain	Moderate Pain	Severe Pain	Intolerable Pain
Ketorolac 0.4%	13.3	25.3	21 3	33.3	6.7
Vehicle	1 3	2.6	14.3	59.7	22 1

Pain Severity

The p-value was < 0 001.

Treatment Group Comparisons
First 12-hour Post-PRK Period Pain Intensity Scores – Categorical Scale (0-4)

	Ketorolac 0 4% (N=77)	Vehicle (N=79)
N	75[b]	77[c]
Mean	1.9	3.0
Median	2 0	3 0
SD[a]	1.18	0 77

[a] Standard Deviation
[b] Two patients were excluded from the analysis. Patient 3379-1066 and Patient 3751-1020 did not have pain intensity recorded during the first 12-hour post-PRK surgery period
[c] Two patients were excluded from the analysis Patient 3751-1130 did not have pain intensity recorded during the first 12-hour post-PRK surgery period Patient 3753-1097 exited study after receiving study medication and prior to the end of the first 12-hour post-PRK surgery period

Reviewer's Comments:

The difference in the distribution of the subjects in the different pain severity categories between treatment groups is statistically significant in favor of the ketorolac treatment group ($p < 0.001$).

The mean pain intensity score for subjects treated with keterolac 0.4% is 1.1 unit lower than the mean score for subjects treated with vehicle.

The following analyses exclude data from study site #3753:

First 12-hour Post-PRK Period Pain Intensity Scores

Percent of Subjects in Each Pain Severity Category

	No Pain	Mild Pain	Moderate Pain	Severe Pain	Intolerable Pain
Ketorolac 0.4%	14	26.3	22.8	31.6	5.3
Vehicle	1.7	3.4	15.3	57 6	22

Pain Severity

The p-value was < 0.001.

Treatment Group Comparisons
First 12-hour Post-PRK Period Pain Intensity Scores – Categorical Scale (0-4)

	Ketorolac 0.4% (N=77)	Vehicle (N=79)
N	59[b]	60[c]
Mean	1.9	2.9
Median	2.0	3.0
SD[a]	1.17	0.82

[a] Standard Deviation
[b] Eighteen patients from study site #3753 were excluded from the analysis.
[c] Nineteen patients from study site #3753 were excluded from the analysis

Reviewer's Comments:

Excluding the data from study site #3753, the difference in the distribution of subjects in the different pain severity categories is statistically significant in favor of the ketorolac treatment group (p<0.001).

Excluding the data from study site #3753, the mean pain intensity scores for subjects treated with ketorolac 0.4% is 1.0 unit lower than the mean score for subjects treated with vehicle.

The results of the two analyses (with and without data from study site #3753) are similar

Study #2 **Protocol No. 191578-003** **Conducted 9/21/01 to 12/24/01**

Title: A Multi-Center, Randomized, Double-Masked, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Analgesic Efficacy of Ketorolac Tromethamine 0.4% Ophthalmic Solution in Post-Photorefractive Keratectomy Patients

Study Design: The study design was identical to Study #1, Protocol No. 191578-002

Test Drug Schedule: Same as Study #1

Investigator Number	Investigator	Number Randomized
3829	**David Hardten, M.D.** Minneapolis, MN 55404 USA	9
3801	**David Markoff, M.D.** Clyde, NC 28721 USA	20
3508	**Matthew Paul, M.D.** Danbury, CT 06810 USA	39
1345	**Frank Price, M.D.** Indianapolis, IN 46260 USA	32
2294	**Kerry D. Solomon, M.D.** Mt. Pleasant, SC 13210 USA	31
3754	**Elizabeth Tonon, M.D.** Portsmouth, VA 23708 USA	17
3755	**John Wittpenn, M.D.** Stonybrook, NY 11790 USA	9

Reviewer's Comments:

It is preferable to have at least 10 patients per arm per center.

A number of patients at study site # 3508 (Principal Investigator - Matthew Paul) were given regular [redacted] instead of [redacted] as escape medication.

Study Design

The study design was identical to Study #1, Protocol No. 191578-002.

Study Medications

- Ketorolac tromethamine 0.4% ophthalmic solution (Allergan formulation number 9437X).
- Vehicle of ketorolac tromethamine 0.4% ophthalmic solution (Allergan formulation number 9439X).

Subject Disposition and Demographics

All 157 randomized subjects received treatment and 147 subjects completed the study.

Subject Disposition

	Number of Subjects		
	Ketorolac 0.4% N (%)	Vehicle N (%)	Total N (%)
Randomized	79	78	157
Discontinued prematurely	1(1.3)	9 (11 5)	10 (6 4)
Included in safety evaluations	79 (100.0)	78 (100.0)	157 (100.0)
Included in intent-to-treat efficacy analysis	79 (100.0)	78 (100 0)	157 (100 0)
Included in per protocol efficacy analysis	51(64.6)	42 (53 8)	93 (59 2)

Reviewer's Comments:

The agency requested the applicant to demonstrate that the protocol deviations associated with study site #3508 did not adversely impact the data. The applicant performed a sensitivity analysis and analyzed the pain intensity for the intent-to-treat population with and without the data from this study site.

Summary of Reasons for Premature Discontinuation from Study

	Number (%) of Subjects		
	Ketorolac 0.4% (N=79) N (%)	Vehicle (N=78) N (%)	Total (N=157) N (%)
Adverse events	1 (1.3)	6 (7.7)	7 (4.5)
Protocol violations		1 (1 3)	1 (0.6)
Other reasons		2 (2.6)	2 (1.3)
Total	1 (1.3)	9 (11.5)	10 (6.4)

Discontinued Patients and Reasons

Investigator	Patient	Treatment	Reason
3801	2072	Vehicle	Adverse events – corneal infiltrates
3754	2119	Vehicle	Protocol violations – non-compliance
3508	2037	Ketorolac 0.4%	Adverse events – conjunctival hyperemia, eye pain, eye edema
	2192	Ketorolac 0.4%	Adverse events – eye pain
	2042	Vehicle	Adverse events – eye pain
	2048	Vehicle	Adverse events – eye pain
	2146	Vehicle	Other
	2152	Vehicle	Adverse events – eye pain
	2189	Vehicle	Adverse events – rhinitis

Investigator	Patient	Treatment	Reason
	2195	Vehicle	Adverse events – eye pain
2294	2186	Vehicle	Other

Summary of Demographic Characteristics (Intent-to-Treat)

		Ketorolac) 0.4% (N=79)	Vehicle (N=78)	Total (N=157)	p-value [a]
Age (Years)	N	79	78	157	0.841
	Mean	39.2	38 6	38.9	
	SD	10.11	9.18	9.63	
	Median	39.0	38 0	38 0	
	Min	21	20	20	
	Max	66	56	66	
Sex	N	79	78	157	0 173
	Male	29 (36 7%)	37 (47 4%)	66 (42.0%)	
	Female	50 (63.3%)	41 (52 6%)	91 (58.0%)	
Race	N	79	78	157	0.879
	Caucasian	73 (92.4)	75 (96.2%)	148 (94.3%)	
	Black	3 (3.8%)	2 (2 6%)	5 (3.2%)	
	Asian	1 (1.3%)	0 (0 0%)	1 (0.6%)	
	Hispanic	1 (1.3%)	1 (1 3%)	2 (1.3%)	
	Other [b]	1 (1.3%)	0 (0.0%)	1 (0.6%)	
Eye Color	N	79	78	157	0.756
	Blue	23 (29.1%)	26 (33.3%)	49 (31.2%)	
	Brown	29 (36.7%)	23 (29.5%)	52 (33.1%)	
	Green	12 (15.2%)	11 (14.1%)	23 (14.6%)	
	Hazel	15 (19 0%)	18 (23 1%)	33 (21.0%)	

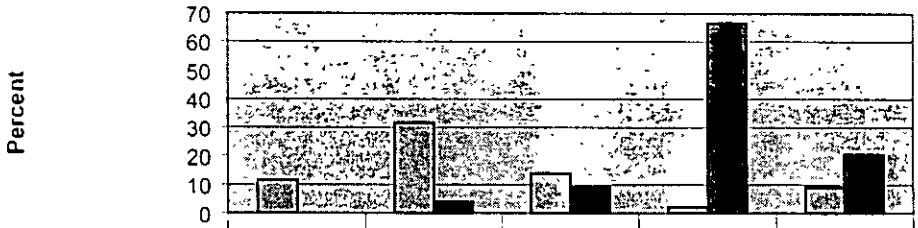
[a] p-value for age is from Wilcoxon rank sum test.
p-values for sex, race, and iris color are from Pearson's chi-square test (or Fisher's exact if >50% of cells have expected count <5)
[b] 'Other' race includes 'Caucasian Native Indian Black'.

Efficacy **Intent-to-Treat Population**

Efficacy analyses with and without data from study site #3508 (Principal Investigator – Matthew Paul) were performed.

The following analyses include data from study site #3508:

Percent of Subjects in Each Pain Severity Category



	No Pain	Mild Pain	Moderate Pain	Severe Pain	Intolerable Pain
Ketorolac 0.4%	11 4	31.6	13.9	2	8 9
Vehicle	0	3.8	9	66.7	20 5

Pain Severity

The p-value was < 0.001.

Treatment Group Comparisons
First 12-hour Post-PRK Period Pain Intensity Scores – Categorical Scale (0-4)

	Ketorolac 0.4% (N=79)	Vehicle (N=78)
N	79	78
Mean	2.0	3.0
Median	2.0	3.0
SD*	1 22	0.67

*Standard Deviation

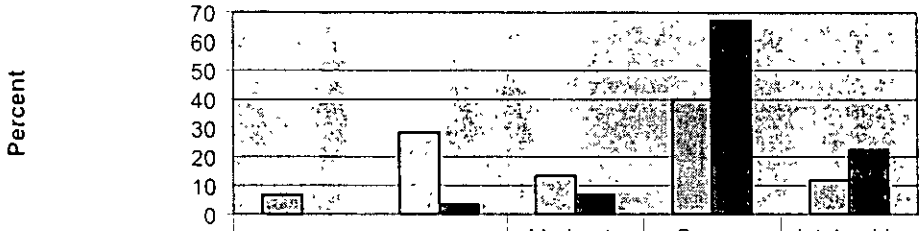
Reviewer's Comments:

The difference in the distribution of the subjects in the different pain severity categories between treatment groups is statistically significant in favor of the ketorolac treatment group (p < 0.001).

The mean pain intensity score for subjects treated with ketorolac 0.4% is 1.0 unit lower than the mean score for subjects treated with vehicle.

The following analyses exclude data from study site #3508:

Percent of Subjects in Each Pain Severity Category



	No Pain	Mild Pain	Moderate Pain	Severe Pain	Intolerable Pain
Ketorolac 0.4%	6.7	28 3	13.3	40	11 7
Vehicle	0	3.4	6.9	67.2	22.4

Pain Severity

The p-value was < 0.001

Treatment Group Comparisons
First 12-hour Post-PRK Period Pain Intensity Scores – Categorical Scale (0-4)

	Ketorolac 0.4% (N=79)	Vehicle (N=78)
N	60	58
Mean	2.2	3.1
Median	3.0	3.0
SD[1]	1 18	0 66

[1] Standard Deviation

Reviewer's Comments:

Excluding the data from study site #3508, the difference in the distribution of subjects in the different pain severity categories is statistically significant in favor of the ketorolac treatment group (p< 0.001).

Excluding the data from study site #3508, the mean pain intensity scores for subjects treated with ketorolac 0.4% is 0.9 unit lower than the mean score for subjects treated with vehicle.

The two analyses are essentially the same (with and without the data from investigator/study site #3508).

6.3.2 **Proposed Indication #2:** The reduction of ocular symptoms of [redacted] burning/stinging, [redacted] following refractive surgery.

The following analyses make no adjustments of the p-values for multiple comparisons.

Ocular Symptoms During Treatment Period: Foreign Body Sensation
(ITT)

Study #1 Protocol No. 191578-002

Visit	Severity Category and Descriptive Statistics	Ketorolac 0.4% N=77 N (%)	Vehicle N=79 N (%)	Treatment p-value [a]
Screening	None	75 (97 4)	77 (98 7)	
	Mild	1 (1 3)	1 (1 3)	0 543
	Moderate	1 (1.3)	0 (0 0)	
	N	77 (100 0)	78 (98 7)	
Day 1	None	16 (20 8)	11 (14 1)	
	Trace	11(14.3)	6 (7.7)	<0.001
	Mild	24 (31.2)	13 (16.7)	
	Moderate	21 (27.3)	26 (33 3)	
	Severe	5 (6 5)	22 (28.2)	
	N	77 (100 0)	78 (98.7)	
Day 2	None	18 (23 4)	22 (28.2)	
	Trace	19 (24.7)	15 (19 2)	0.653
	Mild	21 (27 3)	19 (24.4)	
	Moderate	9 (11.7)	16 (20 5)	
	Severe	10 (13.0)	6 (7.7)	
	N	77 (100.0)	78 (98.7)	
Day 3	None	31 (40.3)	34 (43.6)	
	Trace	28 (36.4)	29 (37.2)	0 683
	Mild	9 (11.7)	4 (5.1)	
	Moderate	5 (6.5)	8 (10.3)	
	Severe	4 (5.2)	3 (3.8)	
	N	77 (100 0)	78 (98 7)	

Study #2 Protocol No. 191578-003

Visit	Severity Category and Descriptive Statistics	Ketorolac 0.4% N=79 N (%)	Vehicle N=78 N (%)	Treatment p-value [a]
Screening	None	76 (96 2)	77 (98.7)	
	Trace	3 (3 8)	1 (1.3)	0.352
	N	79 (100 0)	78 (100 0)	
Day 1	None	17 (21 5)	10 (12.8)	
	Trace	12(15.2)	5 (6.4)	0 005
	Mild	19 (24.1)	20 (25.6)	
	Moderate	26 (32.9)	26 (33.3)	
	Severe	5 (6.3)	17 (21.8)	
	N	79 (100.0)	78 (100.0)	
Day 2	None	12 (15.2)	15 (19.2)	
	Trace	18 (22.8)	13 (16.7)	0.391
	Mild	28 (35.4)	19 (24.4)	
	Moderate	14 (17.7)	23 (29.5)	
	Severe	7 (8.9)	8 (10.3)	
	N	79 (100.0)	78 (100.0)	
Day 3	None	23 (29.1)	33 (42.3)	
	Trace	25 (31.6)	19 (24.4)	0.200
	Mild	19 (24.1)	12 (15.4)	
	Moderate	10 (12.7)	11(14.1)	
	Severe	2 (2.5)	3 (3.8)	
	N	79 (100.0)	78 (100.0)	

Ocular Symptoms During Treatment Period: Photophobia
(ITT)

Study #1 Protocol No. 191578-002

Visit	Severity Category and Descriptive Statistics	Ketorolac 0 4% N=77 N (%)	Vehicle N=79 N (%)	Treatment p-value [a]
Screening	None	74 (96 1)	72 (92.3)	0 245
	Trace	2 (2.6)	3 (3 8)	
	Mild	1 (1 3)	0 (0 0)	
	Moderate	0 (0 0)	3 (3 8)	
	N	77 (100 0)	78 (98 7)	
Day 1	None	9 (11.7)	6 (7 7)	0.018
	Trace	6 (7.8)	1 (1 3)	
	Mild	22 (28 6)	18 (23.1)	
	Moderate	22 (28 6)	26 (33 3)	
	Severe	18(23.4)	27 (34 6)	
	N	77 (100 0)	78 (98 7)	
Day 2	None	11 (14 3)	14 (17 9)	0 825
	Trace	14 (18.2)	9 (11 5)	
	Mild	19 (24 7)	14 (17 9)	
	Moderate	20 (26 0)	14 (17 9)	
	Severe	6 (7 8)	7 (9.0)	
	N	77 (100.0)	78 (98.7)	
Day 3	None	20 (26.0)	23 (29.5)	0 641
	Trace	16 (20 8)	20 (25.6)	
	Mild	20 (26 0)	14 (17 9)	
	Moderate	15 (19.5)	14 (17 9)	
	Severe	6 (7.8)	7 (9 0)	
	N	77 (100 0)	78 (98 7)	

Study #2 Protocol No. 191578-003

Visit	Severity Category and Descriptive Statistics	Ketorolac 0 4% N=79 N (%)	Vehicle N=78 N (%)	Treatment p-value [a]
Screening	None	77 (97.5)	75 (96.2)	0.676
	Trace	0 (0.0)	2 (2.6)	
	Mild	1 (1.3)	1 (1.3)	
	Moderate	1 (1.3)	0 (0.0)	
	N	79 (100.0)	78 (100 0)	
Day 1	None	10 (12.7)	2 (2.6)	<0 001
	Trace	9 (11.4)	3 (3.8)	
	Mild	23 (29.1)	11 (14 1)	
	Moderate	24 (30.4)	38 (48.7)	
	Severe	13(16 5)	24 (30.8)	
	N	79 (100.0)	78 (100.0)	
Day 2	None	13 (16.5)	7 (9.0)	0 073
	Trace	13 (16.5)	10 (12.8)	
	Mild	24 (30.4)	23 (29 5)	
	Moderate	18 (22.8)	26 (33.3)	
	Severe	11 (13.9)	12 (15.4)	
	N	79 (100 0)	78 (100.0)	
Day 3	None	19 (24.1)	19 (24.4)	0.721
	Trace	19 (24.1)	15 (19.2)	
	Mild	19 (24.1)	24 (30.8)	
	Moderate	19 (24.1)	16 (20.5)	
	Severe	3 (3.8)	4 (5.1)	
	N	79 (100 0)	78 (100.0)	

Ocular Symptoms During Treatment Period: Burning/Stinging
(ITT)

Study #1 Protocol No. 191578-002

Visit	Severity Category and Descriptive Statistics	Ketorolac 0 4% (N=77) N (%)	Vehicle N=79 N (%)	Treatment p-value [a]
Screening	None	74 (96 1)	74 (94 9)	
	Trace	3 (3 9)	2 (2 6)	0 598
	Mild	0 (0.0)	1 (1 3)	
	Moderate	0 (0 0)	1 (1.3)	
	N	77 (100 0)	78 (98.7)	
Day 1	None	25 (32 5)	17 (21.8)	
	Trace	14 (18 2)	7 (9 0)	0 002
	Mild	22 (28.6)	21 (26.9)	
	Moderate	14 (28.6)	15 (19 2)	
	Severe	2 (2 6)	18 (23 1)	
	N	77 (100 0)	78 (98 7)	
Day 2	None	29 (37 7)	34 (43 6)	
	Trace	23 (29 92)	16 (20.5)	0 804
	Mild	11 (14 3)	16 (20.5)	
	Moderate	9 (11.7)	9 (11 5)	
	Severe	5 (6 5)	3 (3.8)	
	N	77 (100.0)	78 (98 7)	
Day 3	None	45 (58 4)	57 (73.1)	
	Trace	15 (19.5)	11 (14.1)	0 076
	Mild	10 (13.0)	5 (6.4)	
	Moderate	5 (6.5)	3 (3.8)	
	Severe	2 (2.6)	2 (2.6)	
	N	77 (100.0)	78 (98.7)	

Study #2 Protocol No. 191578-003

Visit	Severity Category and Descriptive Statistics	Ketorolac 0 4% (N=79) N (%)	Vehicle N=78 N (%)	Treatment p-value [a]
Screening	None	78 (98.7)	77 (98.7)	
	Trace	1(1 3)	0 (0)	0 972
	Mild	0 (0.0)	1 (1.3)	
	N	79 (100 0)	78 (100.0)	
Day 1	None	26 (32.9)	15 (19.2)	
	Trace	16 (20 3)	9 (11.5)	<0 001
	Mild	14 (17.7)	13 (16.7)	
	Moderate	21 (26.6)	23 (29.5)	
	Severe	2 (2.5)	18 (23.1)	
	N	79 (100.0)	78 (100.0)	
Day 2	None	30 (38.0)	33 (42.3)	
	Trace	12 (15.2)	16 (20.5)	0 295
	Mild	21 (26.6)	16 (20.5)	
	Moderate	11 (13.9)	9 (11.5)	
	Severe	5 (6.3)	4 (5.1)	
	N	79 (100.0)	78 (100.0)	
Day 3	None	53 (67.1)	56 (71.8)	
	Trace	15 (19 0)	6 (7.7)	0.647
	Mild	6 (7.6)	9 (11.5)	
	Moderate	4 (5.1)	5 (6.4)	
	Severe	1 (1.3)	2 (2.6)	
	N	79 (100.0)	78 (100.0)	

Ocular Symptoms During Treatment Period: Tearing (ITT)

Study #1 Protocol No. 191578-002

Visit	Severity Category and Descriptive Statistics	Ketorolac 0.4% N=77 N (%)	Vehicle N=79 N (%)	Treatment p-value [a]
Screening	None	74 (96.1)	77 (98.7)	
	Trace	3 (3.9)	1 (1.3)	0.272
	N	77 (100.0)	78 (98.7)	
Day 1	None	11 (14.3)	2 (2.6)	
	Trace	7 (9.1)	7 (9.0)	0.001
	Mild	19 (24.7)	11 (14.1)	
	Moderate	23 (29.9)	27 (34.6)	
	Severe	17(22.1)	31 (39.7)	
	N	77 (100.0)	78 (98.7)	
Day 2	None	19 (24.7)	19 (24.4)	
	Trace	18 (23.4)	17 (21.8)	0.393
	Mild	17 (22.1)	14 (17.9)	
	Moderate	19 (24.7	21 (26.9)	
	Severe	4 (5.2)	7 (9.0)	
	N	77 (100.0)	78 (98.7)	
Day 3	None	33 (42.9)	34 (43.6)	
	Trace	17 (22.1)	20 (25.6)	0.694
	Mild	15 (19.5)	13 (16.7)	
	Moderate	11 (14.3)	9 (11.5)	
	Severe	1 (1.3)	2 (2.6)	
	N	77 (100.0)	78 (98.7)	

Study #2 Protocol No. 191578-003

Visit	Severity Category and Descriptive Statistics	Ketorolac 0.4% N=79 N (%)	Vehicle N=78 N (%)	Treatment p-value [a]
Screening	None	77 (97.5)	77 (98.7)	
	Trace	2 (2.5)	1 (1.3)	0.683
	N	79 (100.0)	78 (100.0)	
Day 1	None	24 (30.4)	11 (14.1)	
	Trace	6 (7.6)	4 (5.1)	0.004
	Mild	12 (15.2)	10 (12.8)	
	Moderate	22 (27.8)	31 (39.7)	
	Severe	15 (19.0)	22 (28.2)	
	N	79 (100.0)	78 (100.0)	
Day 2	None	25 (31.6)	16 (20.5)	
	Trace	14 (17.7)	17 (21.8)	0.651
	Mild	17 (22.5)	29 (37.2)	
	Moderate	18 (22.8)	12 (15.4)	
	Severe	5 (6.3%)	4 (5.1)	
	N	79 (100.0)	78 (100.0)	
Day 3	None	41 (51.9)	40 (51.3)	
	Trace	18 (22.8)	20 (25.6)	0.824
	Mild	12 (15.2)	13 (16.7)	
	Moderate	6 (7.6)	4 (5.1)	
	Severe	2 (2.5)	1 (1.3)	
	N	79 (100.0)	78 (100.0)	

[a] P-values are from Cochran-Mantel-Haenszel test for row mean score differences with modified ridits, stratified by investigator.

For the ocular symptom, itching, there are no significant differences between treatment groups at any of the visits during the treatment period for Study #1 ($p \geq 0.585$) and Study #2 ($p \geq 0.444$).

Reviewer's Comments:

Ocular symptom (foreign body sensation, photophobia, burning/ stinging, tearing, and itching) is one of four broad categories of secondary efficacy variables that are pre-specified in Protocols 191578-002 and 191578-003. Testing of multiple parameters are performed. After the appropriate statistical adjustments are made for multiple comparisons, only one ocular symptom, burning/stinging, shows a statistical significant difference between treatment groups in favor of ketorolac 0.4% that is confirmed in the second study (p must be ≤0.003 (0.05/16) in each study).

6.4 The submitted studies in NDA 21-528 are sufficient to establish efficacy for the use of ketorolac 0.4% in the reduction of post-operative pain following PRK surgery. Statistical and clinical significance for this endpoint are demonstrated in two controlled clinical studies

The submitted studies in NDA 21-528 are sufficient to establish efficacy for the use of ketorolac 0.4% in the reduction of burning/stinging following PRK surgery. After the appropriate statistical adjustments are made for multiple comparisons, statistical significance between treatment groups in favor of ketorolac 0.4% was demonstrated in Protocol 191578-002 and confirmed in Protocol 191578-003.

The submitted studies in NDA 21-528 are not sufficient to establish efficacy for the use of ketorolac 0.4% in the reduction of foreign body sensation, photophobia, and tearing following PRK surgery. After the appropriate statistical adjustments are made for multiple comparisons in Protocols 191578-002 and 191578-003, there was no difference between treatment groups for the following ocular symptoms: foreign body sensation, photophobia, and tearing.

7 Integrated Review of Safety

7.1 The submitted studies in NDA 21-528 indicate that the safety profile of ketorolac 0.4% is similar to the currently the approved and marketed products, Acular 0.5% and Acular PF. Similar to Acular PF, ketorolac 0.4% is associated with delayed wound healing. The most frequent adverse event that was reported with the use of ketorolac 0.4% (4.0-5.0%) was eye pain.

7.2 The safety database consists of safety data from two clinical trials, Protocols191578-002 and 191578-003.

7.3 The safety database consists of 313 post-PRK surgery subjects from two clinical studies (Protocols 191578-002 and 191578-003). The number of subjects exposed to ketorolac 0.4% was 156 and 157 for vehicle. The dose of the study medication was 1 drop to the study eye QID up to 4 days. The mean duration of treatment exposure (range 1 to 6 days) was 3.7 days for the ketorolac treatment group and 3.5 days for the vehicle treatment group.

7.4 Study #1 Protocol No. 191578-002

Safety

Safety analyses with and without data from study site #3753 (Principal Investigator – Frank Bishop) were performed.

Adverse Events

All 156 subjects who enrolled in the study received treatment and were included in the safety analysis. No deaths or other serious adverse events occurred during the study. Five subjects (6.5%) receiving ketorolac 0.4% and two subjects (2.5%) receiving vehicle prematurely discontinued from the study due to adverse events.

Frequency and Incidence of Ocular and Non-ocular Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	Ketorolac 0.4% (N=77)	Vehicle (N=79)	Total (N=156)
	N (%)	N (%)	N (%)
OCULAR			
Pain eye	4 (5.2))	2 (2 5)	6 (3 8)
Cornea (NOS)	1 (1.3)		1 (0 6)
Corneal infiltrates	1 (1.3)		1 (0 6)
Corneal irritation		1 (1.3)	1 (0.6)
NON-OCULAR			
Body as a whole			
Headache	3 (3.9)	5 (6.3)	8 (5.1)
Chills		1 (1.3)	1 (0.6)
Pain face		1 (1.3)	1 (0 6)
Cardiovascular System			
Syncope	1 (1.3)		1 (0.6)
Digestive System			
Nausea		2 (2.5)	2 (1.3)
Vomiting		2 (2.5)	2 (1.3)
Respiratory System			
Rhinitis	1 (1.3)	1 (1.3)	2 (1.3)
Skin and Appendages			
Sweat		1 (1.3)	1 (0.6)
Special Senses			
Infection ear	1 (1.3)		1 (0.6)

Biomicroscopy

Slit lamp biomicroscopy without pupil dilation was performed on both eye at visit 1 (day −7 to -1), and only on the study eye at follow-up visits 3 through 5 (days 1 through 3). If the patient continues into the post-treatment period (visit 6+), then biomicroscopy was performed at each visit until the patient exited the study. The examinations included evaluation of the lids, conjunctiva, anterior chamber, cornea, and lens. Observations were graded using a 5-point scale (0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe).

The following analysis includes data from study site #3753:

Number (%) of Patients with at Least 1 Severity Grade Increase from Baseline at the Final Study Visit Occurring at Rates Greater than 5%

Finding	Ketorolac 0.4% N=77	Vehicle N=79
N (%)	77 (100.0)	78 (98.7)
Conjunctival erythema	31 (40.3)	38 (48.7)
Lid edema	17 (22.1)	25 (32.1)
Lid erythema/hyperemia	13 (16.9)	20 (25.6)
Corneal edema	12 (15.6)	13 (16.7)
Corneal staining/erosion	10 (13 0)	7 (9 0)
Conjunctival chemosis	4 (5.2)	7 (9.0)

The following analysis excludes data from study site #3753:

Number (%) of Patients with at Least 1 Severity Grade Increase from Baseline at the Final Study Visit Occurring at Rates Greater than 5%

Finding	Ketorolac 0.4% N=77	Vehicle N=79
N (%)	59 (76.6)	60 (75.9)
Conjunctival erythema	26 (44.1)	31 (51.7)
Lid edema	16 (27.1)	23 (38.3)
Lid erythema/hyperemia	12 (20.3)	14 (23.3)
Corneal edema	12 (20.3)	11 (18.3)
Corneal staining/erosion	9 (15.3)	6 (10.0)
Conjunctival chemosis	3 (5.1)	6 (10 0)

Reviewer's Comments:

The results of the two analyses (with and without data from study site #3753) are similar.

Visual Acuity

Best-corrected visual acuity using ETDRS chart was measured for each eye at visit 1 (day −7 to day −1), and only the study eye at visit 5 (day 3) or at the patient's exit visit.
The following analysis included data from study site #3753:

Change in Visual Acuity from Baseline to Final Visit

Line Changes	Ketorolac 0.4% (N=77)	Vehicle (N=79)	p-value [a]
N (%)	76 (98.7)	75 (94.9)	0.456
≥ 2 lines loss	60 (78.9)	57 (76.0)	
1 line loss	10 (13.2)	11 (14.7)	
No Change	5 (6.6)	7 (9.3)	
1 line gain	0 (0.0)	0 (0.0)	
≥ 2 lines gain	1 (1.3)	0 (0.0)	

[a] P-value is from Cochran-Mantel-Haenszel test for row mean score differences with modified ridits, stratified by investigator

Reviewer's Comments:

At the final visit, almost seventy-nine percent (78.9%) of subjects from the ketorolac treatment group and seventy-six percent (76.0%) of subjects from the vehicle treatment group experienced a two lines or greater loss of visual acuity.

The following analysis excludes data from study site #3753:

Change in Visual Acuity from Baseline to Final Visit

Line Changes	Ketorolac 0.4% (N=77)	Vehicle (N=79)	p-value [a]
N (%)	59 (76.6)	57 (72.2)	0.252
≥ 2 lines loss	44 (74.6)	41 (71.9)	
1 line loss	9 (15.3)	10 (17.5)	
No Change	5 (8.5)	6 (10.5)	
1 line gain	0 (0.0)	0 (0.0)	
≥ 2 lines gain	1 (1.7)	0 (0.0)	

[a] P-value is from Cochran-Mantel-Haenszel test for row mean score differences with modified ridits, stratified by investigator.

Reviewer's Comments:

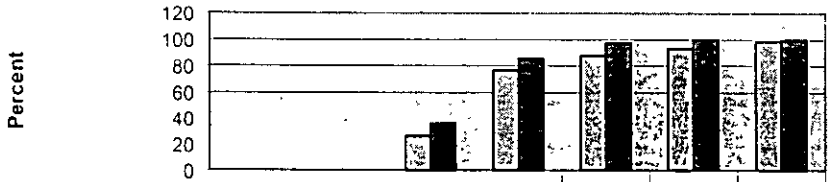
The results of the two analyses (with and without data from study site #3753) are similar.

Corneal Re-epithelialization

Corneal re-epithelialization was evaluated (complete/incomplete) for the study eye at each study visit after visit 2 (day 0/PRK) during the treatment period. If the patient continued into the post-treatment period (visit 6+/incomplete re-epithelialization), then corneal re-epithelialization was evaluated at each visit until the patient exited the study (complete re-epithelialization).

The following analysis included data from study site #3753:

Percent of Subjects with Complete Re-epithelialization Over Time



	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Ketorolac 0 4%	0	0	26 3	76 4	87 5	93	98 3
Vehicle	0	0	35 5	85 2	97 3	100	100

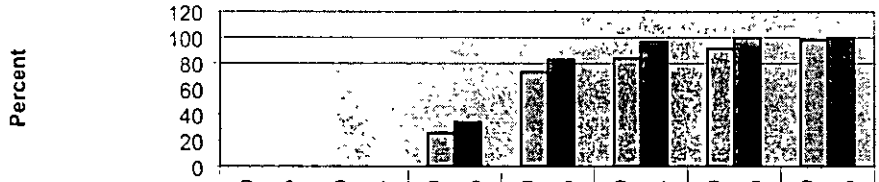
Treatment Period (Days 0-3)/Post-Treatment Period (Days 4+)

Reviewer's Comments:

The percentage of subjects treated with ketorolac 0.4% with complete re-epithelialization of the cornea is consistently lower than the percentage of subjects treated with vehicle through out the post-PRK surgery period (treatment and post-treatment periods).

The following analysis excludes the data from study site #3753:

Percent of Subjects with Complete Re-epithelialization Over Time



	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Ketorolac 0 4%	0	0	25.9	72.9	83.7	91	97.7
Vehicle	0	0	33.9	82.6	96.5	100	100

Treatment Period (Days 0-3)/Post-Treatment Period (Days 4+)

Reviewer's Comments:

The results from the two analyses (with and without the data from study site #3753) are similar.

Study #2 **Protocol No. 191578-003**

Safety

Adverse Events

All 157 subjects who enrolled in the study received treatment and were included in the safety analysis. No deaths or other serious adverse events occurred during the study. One subject (1.3%) receiving ketorolac 0.4% and nine subjects (11.5%) receiving vehicle prematurely discontinued from the study due to adverse events.

Frequency and Incidence of Ocular and Non-ocular Adverse Events
Occurring at Rates Greater than 1%

Coded Adverse Event	Ketorolac 0.4% (N=79)	Vehicle (N=78)	Total (N=157)
	N (%)	N (%)	N (%)
OCULAR			
Pain eye	3 (3.8)	4 (5.1)	7 (4.5)
Cornea infiltrates	1 (1.3)	1 (1.3)	2 (1.3)
Edema eye	1 (1.3)		1 (0.6)
Conjunctival hyperemia (NOS)	1 (1.3)		1 (0.6)
Corneal (NOS)		1 (1.3)	1 (0.6)
NON-OCULAR			
Body as a whole			
Headache	1 (1.3)	2 (2.6)	3 (1.9)
Digestive System			
Nausea		3 (3.8)	3 (1.9)
Nausea vomit		2 (2.6)	2 (1.3)
Vomiting		1 (1.3)	1 (0.6)
Respiratory System			
Rhinitis		1 (1.3)	1 (0.6)

Biomicroscopy

Number (%) of Patients with at Least 1 Severity Grade Increase
from Baseline at the Final Study Visit Occurring at Rates Greater than 5%

Finding	Ketorolac 0.4% N=79	Vehicle N=78
N (%)	79 (100.0)	78 (100.0)
Conjunctival erythema	23 (29.1)	37 (47.4)
Corneal staining/erosion	16 (20.3)	19 (24.4)
Lid edema	14 (17.7)	19 (24.4)
Corneal edema	12 (15.2)	14 (17.9)
Lid erythema/hyperemia	6 (7.6)	13 (16.7)
Conjunctival chemosis	2 (2.5)	4 (5.1)

Change in Visual Acuity from Baseline to Final Visit

Line Changes	Ketorolac 0.4% (N=79)	Vehicle (N=78)	p-value [a]
N (%)	78 (98.7)	73 (93.6)	0.820
≥ 2 lines loss	65 (83.3)	60 (82.2)	
1 line loss	7 (9.0)	8 (11.0)	
No Change	2 (2.6)	4 (5.5)	
1 line gain	1 (1.3)	1 (1.4)	
≥ 2 lines gain	3 (3.8)	0 (0.0)	

[a] P-value is from Cochran-Mantel-Haenszel test for row mean score differences with modified ridits, stratified by investigator.

Reviewer's Comments:

At the final visit, eight-three percent (83.3%) of subjects from the ketorolac treatment group and eighty-two percent (82.2%) of subjects from the vehicle treatment group experienced a two lines or greater loss of visual acuity.

Corneal Re-epithelialization

Percent of Subjects with Complete Re-epithelialization Over Time

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Ketorolac 0 4%	0	0	16 5	73.4	97.2	100	100	100
Vehicle	0	2.6	28 3	86.8	98.4	98.4	98.4	100

Treatment Period (Days 0-3)/Post-Treatment Period (Days 4+)

Reviewer's Comments:

During the treatment period (Days 0-3), the percentage of subjects treated with ketorolac 0 4% with complete re-epithelialization of the cornea is lower than the percentage of subjects treated with vehicle.

7.5 There is no pharmacological evidence for any potential for drug abuse with ketorolac 0.4%. No studies have been conducted related to overdosage in humans.

7.6 The agency determined that the safety database from the two submitted clinical studies in NDA 21-528 was adequate. Ketorolac 0.4% is a reformulation of a currently market product, Acular (ketorolac tromethamine ophthalmic solution) 0.5% that has a higher level of active and inactive ingredients than the reformulated product.

7.7 The currently market product, Acular PF 0.5% is labeled with the precaution that the product may impair wound healing. The submitted studies in NDA 21-528 is consistent with indicate that ketorolac 0.4% may impair wound healing.

8 Dosing, Regimen, and Administration Issues

Ketorolac 0.4% is a reformulation of Applicant's current marketed product Acular (ketorolac tromethamine ophthalmic solution) 0.5%. No change to the dosing regimen was proposed in this submission.

9 Use in Special Populations

9.1 Applicant's analyses on the effects of gender, age, race, and ethnicity on efficacy and safety are adequate.

9.2 Applicant requested a pediatric waiver, which was granted.

9.3 No additional data in other special populations are needed.

10 Conclusions, Recommendations, and Labeling

10.1 The submitted studies in NDA 21-528 are sufficient to establish efficacy for the use of ketorolac 0.4% in the reduction of post-operative pain and burning/stinging following PRK surgery. The safety profile of ketorolac 0.4% is similar to that of the previously approved ketorolac tromethamine ophthalmic solutions, Acular 0.5% and Acular PF 0.5%.

10.2 NDA 21-528 is recommended for approval for the reduction of post-operative pain and burning/stinging following PRK surgery.

10.3 *Recommended additions are shown by underlining and recommended deletions are shown by strikethrough lines.*

Number of Pages Redacted 6

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Draft Labeling
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Lucious Lim
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Wiley Chambers
2/19/03 01:53:54 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-528
Labeling Amendments

NDA 21-528
Amendment BL

Submission Date: 9/27/2002, 10/18/2002
Received Date: 9/30/2002, 10/21/2002
Review Date: 10/29/2002

Sponsor:

Allergan, Inc.
2525 Dupont Drive
P. O. Box 19534
Irvine, CA 92623-9534
(714) 246-4391
Contact: Elizabeth Bancroft

Drug:

Ketorolac tromethamine ophthalmic Solution 0.4%

Pharmacologic Category:

Nonsteroidal anti-inflammatory

Dosage Form and Route of Administration:

Ophthalmic solution for topical ocular administration

Submitted:

Submitted are two labeling amendments. In the September 27, 2002 amendment, applicant proposed a tradename of Acular — 0.4% for ketorolac tromethamine ophthalmic solution 0.4%. The October 18, 2002 amendment explained that the — abbreviation in the proposed tradename stands for ' —

Reviewer's Comments:

The proposed tradename is unacceptable. The abbreviation —
— makes an efficacy claim within the tradename. The applicant should submit alternative tradename(s) for consideration.

Lucious Lim, M.D., M.P.H.
Medical Officer

cc: NDA 21-528
HFD-550/Div Files
HFD-550/CSO Rodriguez
HFD-550/Dep Div Dir/Chambers

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Medical Officer's Review of NDA 21-528
Labeling Amendments

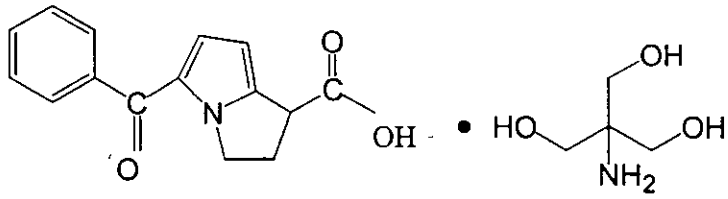
NDA 21-528
Medical Officer's Review

Submission Dates: 5/6/03, 5/9/03, 5/20/03, 5/22/03
Received Dates: 5/7/03, 5/12/03, 5/21/03, 5/23/03
Review Completed: 5/28/03

Proposed Trademark: Acular LS

Generic Name: Ketorolac tromethamine ophthalmic solution 0.4%

Chemical Name:



Mol Wt 376.41
ketorolac tromethamine $C_{19}H_{24}N_2O_6$

(±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

Sponsor:
Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534
(714) 246-4391
Contact: Elizabeth Bancroft

Pharmacologic Category: Nonsteroidal anti-inflammatory

Dosage form and Route of Administration: Ophthalmic solution for topical ocular administration

Number of Pages Redacted 5

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Draft Labeling
(not releasable,

Recommended Regulatory Action:

The above package insert and proposed label and carton are recommended for approval.

Lucious Lim, M.D., M.P.H.
Medical Officer

cc: NDA 21-528
HFD-550/Div Files
HFD-550/BIOPHARM/Tandon
HFD-550/BIOSTATS/Lu
HFD-550/CHEM/Tso
HFD-550/PHARM/Chen
HFD-550/PM/Rodriguez
HFD-047/DSI/Shibuya
HFD-042/DDMAC/Saini
HFD-550/MO/Lim
HFD-550/CTL/Boyd
HFD-550/Dep Div Director/Chambers
HFD-550/Div Director/Simon

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Wiley Chambers
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Medical Officer's Review of NDA 21-528
120-Day Safety Update

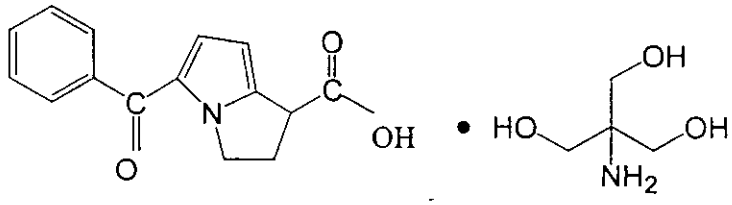
NDA 21-528
Medical Officer's Review

Submission Date: December 6, 2002
Received Date: December 10, 2002
Review Completed: May 28, 2003

Proposed Trademark: Acular LS

Generic Name: Ketorolac tromethamine ophthalmic solution 0.4%

Chemical Name:



Mol Wt 376.41
ketorolac tromethamine $C_{19}H_{24}N_2O_6$

(±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

Sponsor:

Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534
(714) 246-4391
Contact: Elizabeth Bancroft

Pharmacologic Category: Nonsteroidal anti-inflammatory

Dosage form and Route of Administration: Ophthalmic solution for topical ocular administration

Submitted:

Submitted is the 120-day safety update. The update states, "The pivotal Phase 3 studies of the original NDA, clinical studies 191578-002 and 191578-003, were completed and full study reports were submitted in the original submission. There are no additional safety data to report from these studies.

No new preclinical or clinical studies have been planned or conducted during this 120-day reporting period."

Reviewer's Comments:

Agree.

Lucious Lim, M.D., M.P.H.
Medical Officer

cc: NDA 21-528
HFD-550/Div Files
HFD-550/BIOPHARM/Tandon
HFD-550/BIOSTATS/Lu
HFD-550/CHEM/Tso
HFD-550/PHARM/Chen
HFD-550/PM/Rodriguez
HFD-047/DSI/Shibuya
HFD-550/MO/Lim
HFD-550/CTL/Boyd
HFD-550/Dep Div Director/Chambers

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Wiley Chambers
5/28/03 05:04:31 PM
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